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FRONTAL LOBE EPILEPSY, SLEEP AND PARASOMNIAS

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DECLARATION OF AUTHORSHIP AND ORIGINALITY

I, Christopher Paul Derry, confirm that the work presented in this thesis is my own. Where information has been derived form other sources, this is acknowledged in the text.

In particular, for the studies presented in Chapter 11, radiosynthesis of ^{18}F-MPPF was undertaken by Rachel Mulligan at the Austin Hospital and Didier Le Bars in Lyon. The β-microprobe experiment in this study was designed by me, and I was present during the experiments, but these were primarily conducted by Dr Luc Zimmer from CERMEP, Lyon.

Molecular genetic analysis for the families presented in Chapter 14 was undertaken by Ms Sarah Heron and A/Prof J. Mulley at the Department of Genetic Medicine, Women's and Children's Hospital, Adelaide, Australia.

Christopher Paul Derry

DEDICATION

For my wife and best friend,

Natalie

ABSTRACT

A close relationship exists between sleep and epilepsy. While many forms of epilepsy may be influenced by the sleep-wake cycle, this phenomenon is particularly evident in frontal lobe epilepsy where affected individuals may experience seizures exclusively during sleep (nocturnal frontal lobe epilepsy, NFLE). In this thesis, three aspects of the relationship between sleep and frontal lobe epilepsy are examined.

Firstly, serotonergic neurotransmission across the human sleep-wake cycle was studied using the novel PET ligand ^{18}F-MPPF, a serotonergic $5HT_{1A}$ receptor radioligand sensitive to endogenous serotonin release. Fourteen individuals with narcolepsy underwent ^{18}F-MPPF PET scans during sleep and wakefulness. The study demonstrated a 13% increase in ^{18}F-MPPF binding potential ($p<0.01$) during sleep, indicating a reduction in serotoninergic neurotransmission, in line with existing animal data.

Secondly, the characterisation of benign, non-epileptic parasomnias and their distinction from nocturnal frontal lobe seizures was addressed in two studies. The first comprised an analysis of the historical features of these conditions, and included the development and validation of a clinical scale for the diagnosis of nocturnal events. The second comprised a detailed semiological analysis of a series of parasomnias recorded on video-EEG monitoring, and a statistical comparison with seizures in NFLE. Although similarities between NFLE and parasomnias were observed, the results provide an evidence base for the confident distinction of these disorders.

Finally, the familial form of NFLE (autosomal dominant nocturnal frontal lobe epilepsy, ADNFLE) is associated with mutations in genes for nicotinic acetylcholine receptor subunits, but recognised mutations account for only a minority of reported cases. The last study presented here is a clinical and genetic analysis of two large families with an unusually severe ADNFLE phenotype. Affected individuals had refractory epilepsy and increased rates of mental retardation and psychiatric disorders

and, in one family, linkage studies suggest a previously unrecognised underlying mechanism.

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PRIZES AND PEER-REVIEWED PUBLICATIONS

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ABBREVIATIONS AND GLOSSARY OF TERMS

^{18}F	Fluorine radioisotope used in PET scanning
5-HT	Serotonin
$5HT_{1A}$	Serotonin (5-HT) 1A receptor
ACh	Acetylcholine
ADNFLE	Autosomal dominant nocturnal frontal lobe epilepsy
ASDA	American Sleep Disorders Association
B_{max}	Maximum concentration of receptor sites
BP	Binding potential
C_A	Arterial concentration of tracer in PET kinetic modelling
CHRNA2	Neuronal nicotinic acetylcholine receptor alpha 2 subunit gene
CHRNA4	Neuronal nicotinic acetylcholine receptor alpha 4 subunit gene
CHRNB2	Neuronal nicotinic acetylcholine receptor beta 2 subunit gene
CRH	Corticotrophin releasing hormone
CT	Computed tomography
DRN	Dorsal raphe nuclei
EEG	Electroencephalogram
EMG	Electromyography
EOG	Electrooculography
FDG	Fluorodeoxyglucose
FLE	Frontal lobe epilepsy
FLEP scale	Frontal lobe epilepsy and parasomnias scale
GABA	Gamma-amino butyric acid
Glu	Glutamate
IGE	Idiopathic generalised epilepsy
ILAE	International League Against Epilepsy
K_1	Arterial input function in PET kinetic modelling
K_d	Equilibrium dissociation constant of a ligand

LC	Locus coeruleus
LDT	Lateral dorsal tegmental nucleus
LOD	Log of the odds
LOR	Line of response
MPPF	4-2′-(methoxy-phenyl)-1-[2′-(*N*-2″-pyridinyl)-*p*-fluorobenzamido]ethlpiperazine
MRI	Magnetic resonance imaging
M_T	Concentration of tracer in brain in PET kinetic modelling
nAChR	Nicotinic acetylcholine receptor
NFLE	Nocturnal frontal lobe epilepsy
NOR	Noradrenaline
NREM	Non-rapid eye movement
PET	Positron emission tomography
PPT	Pedunculopontine tegmental nucleus
PSG	Polysomnography
R_0	K_1 ratio between reference tissue and tissue of interest
RBD	REM behaviour disorder
rCBF	Regional cerebral blood flow
REM	Rapid eye movement
SPECT	Single photon emission computed tomography
VEM	Video EEG monitoring

PART 1:- LITERATURE REVIEW

CHAPTER 1
HISTORICAL PERSPECTIVE

1a. Early writings

A relationship between sleep and epilepsy has been recognised since antiquity. Some of the earliest writings on epilepsy are from Ancient Greece, and the term 'epilepsy' is derived from the Greek verb *epilambanein,* meaning 'to seize' or 'to attack'. In a volume of his collection of medical writings entitled 'On the Sacred Disease', written around 400 BC, Hippocrates rejected the commonly held belief that seizures were manifestations of divine or demonic possession (Temkin, 1994). He proposed a physiological rather than a supernatural basis for seizures, and stated that the allegedly divine character of epilepsy was a shelter for the fraudulent practices of magicians and charlatans. He therefore emphasised the importance of diet and drugs in the treatment of epilepsy, as opposed to exorcism, and recognised the importance of regular sleep in the prevention of seizures. Patients should "spend the day awake and the night asleep. If this habit be disturbed, it is not so good....worst of all is when he sleeps neither night nor day" (Temkin, 1994). Other influential physicians from Ancient times also noted the relationship between seizures and sleep. Aristotle declared that "sleep is like epilepsy and, in a sense, actually is a seizure of sorts. Accordingly, the beginning of this malady takes place with many during sleep, and their subsequent habitual seizures occur during sleep and not in waking hours" (Aristotle, 350 BC). Galen, whose teachings formed the cornerstone of Western medicine until the Enlightenment in the 17th century, warned against sleeplessness, and Aretaeus (2nd century AD) emphasised the need for regular sleep patterns in his complex health regimes for sufferers of epilepsy (Temkin, 1994).

In ancient writings, a distinction was drawn between epilepsy and other events arising from sleep such as parasomnias, although the conditions were often linked. Hippocrates reported "people groaning and shouting in their sleep....others jump from their bed and run outside and remain out of their mind until they wake, when they are as healthy and sane as they were before" (Temkin, 1994). Soranus (2nd

century AD), on the other hand, stated that untreated nightmares would result in epilepsy, and Posidonius taught that "what epileptics suffer in their attacks when awake, sufferers from incubus undergo in their sleep'(Temkin, 1994).

In the Middle Ages, however, medical beliefs and practices became heavily influenced by the rise of Christianity, and the rational observation of the Greeks and Romans was replaced by religiosity and mysticism. Epilepsy, along with parasomnias and madness, was often considered to be the result of demonic possession, and was widely known as "the falling evil". The term incubus, which is now associated with an adult parasomnia, was coined in this era and derives from the Latin 'incubo' meaning 'to lie upon'. An incubus was a lascivious male demon which would possess mortal women as they slept, sexually assaulting them. These demons were of considerable concern to the medieval church, and were discussed in the writings of St Augustine (354-430 AD) and Thomas Aquinas (1225-1274 AD). Likewise, the demonic nature of epilepsy seems to have been confirmed in a famous passage from the Gospel of St Mark, (ix 14-29) in which Jesus drives out a 'foul spirit' from a possessed boy. In this passage, the father of the possessed boy describes how his son 'Hath a dumb spirit; and wheresoever he taketh him, he teareth him: and he foameth, and gnasheth with his teeth, and pineth away....and oftentimes it hath cast him into the fire, and into the waters, to destroy him'. Jesus witnesses such an attack, and rebukes the spirit, driving it out of the boy. The description sounds very much like a seizure, and the interpretation given in the Gospel was widely accepted by the Church. In the third century AD, the Christian theologian Origen wrote 'We... believe the Gospel in the point that this disease, in those affected with it, is obviously brought about by an unclean dumb and deaf spirit' (Temkin, 1994). Such views prevailed, and the treatment for epilepsy therefore was based on regimes of prayer and fasting, often in conjunction with bleeding, purging, vomiting and, in severe cases, trephining.

Little progress was made until the Enlightenment in the 17th and 18th centuries heralded a return to a rational and methodological approach to medicine. Landmark discoveries in the field of medicine were made in this period, such as William Harvey's demonstration of cardiovascular circulation, and physicians began to emphasise the importance of detailed descriptions and systematic

classification of diseases. The principles of clinical neurology began to develop at this time under Thomas Willis and Thomas Sydenham, and new theories of epilepsy began to develop. Willis hypothesised that in seizures a 'spasmodic copula' distilled from the blood to the brain causing the animal spirits there to explode, manifesting as a seizure (Willis, 1684). This concept of an explosion of animal spirits in the brain was a new way of explaining epilepsy, and clearly an advance from a scientific perspective, but was only one of a variety of theories circulating at that time. Unfortunately, while these ideas resulted in a change in the conceptualisation of epilepsy, they were not accompanied by any significant improvement in therapeutics.

1b. Emergence of modern concepts

By the 19th century the practice of clinical neurology was well established. The work of Hughlings Jackson led to a concept of epilepsy which gradually gained widespread acceptance. He drew upon both an increasing physiological knowledge at the time and careful clinical descriptions of seizures, defining epilepsy as "a chronic disorder in which there are recurring, sudden, excessive, and rapid discharges of grey matter of some parts of the brain, the clinical manifestations of which are determined by the anatomical site in the brain of the discharge" (Jackson, 1873). Considerable work on the relationship of seizures to sleep was undertaken on institutionalised patients in this period. In a seminal study of 840 such patients, William Gowers reported that 21% had seizures exclusively at night, 42% exclusively in the day, and the remaining 37% in either day or night (Gowers, 1885). In this era of painstaking clinical evaluation and diagnosis, there was considerable debate as to whether parasomnias such as confusional arousals and sleepwalking represented variants of nocturnal epilepsy or were separate conditions altogether. While some authors distinguished between sleepwalking and epilepsy (Echeverria, 1879), others were less sure. Prichard, for example, believed that epilepsy, somnambulism and incubus were similar afflictions, and stated "where they do not coexist with epilepsy they often seem to stand in the place of it" (Temkin, 1994). With only clinical observation as a guide, there was significant doubt as to the possible epileptic nature of these and

many other 'minor' symptoms such as vertigo, chorea and cataplexy, which Gelineau reported in his description of narcolepsy in 1880 (Gelineau, 1880).

1c. Development of electroencephalography

Towards the turn of the century, there was increasing interest in the importance of electricity in the functioning of the brain. The discovery of spontaneous, continuous and recordable electrical currents in the brain was made by Richard Caton in 1875. Caton studied the brains of rabbits and monkeys, investigating the electrical response to external sensory stimulation. He reported that 'in every brain hitherto examined, the galvanometer has indicated the existence of feeble electric currents...of variable direction". (Caton, 1875, 1877). Meanwhile the physicians Fritsch and Hitzig in Berlin had demonstrated that electrical stimulation of the brains of dogs produced replicable motor responses in certain areas of the brain, and in some animals this stimulation resulted in epileptic seizures (Fritsch, 1963). Together, these findings implicated electrical activity in both the normal function of the brain and in seizures and were a prelude to the most important technical development in epileptology and sleep medicine, the invention of the electroencephalogram. The Austrian psychiatrist Hans Berger published the first of a series of papers entitled 'Uber das Elektroenkephalogram' in 1929 (Friedlander, 2001). Berger himself noted changes in the EEG during sleep, and these changes were subsequently divided into 'stages' by Loomis et al in 1939. In the 1960s this was modified and standardised into the sleep staging system used today (Rechstaffen, 1968). In the interim, the discovery of rapid eye movement (REM) sleep by Aserinsky and Kleitman in 1953 had revolutionised the concept of sleep; it was no longer thought of as simply a passive state of brain inactivity, but rather as an active, dynamic process.

The EEG was rapidly established as an important tool in the evaluation of patients with epilepsy, revealing characteristic electrical 'epileptiform' discharges in many subjects. In addition, it soon became apparent that the clinical relationship observed between sleep and epilepsy had an EEG correlate. Gibbs and Gibbs reported activation of epileptiform discharges in sleep (Gibbs, 1947), although it was subsequently recognised that, while NREM sleep was an activator, REM

sleep suppressed generalised epileptiform discharges (Sato et al., 1973) . Subsequently Rodin demonstrated the activating potential of sleep deprivation on the EEG (Rodin, 1962).

1d. Neurotransmitters and sleep

While the electroencephalogram revolutionised the study of the neurophysiology of sleep and epilepsy, animal studies from the 1930s started to shed light on the neurochemical changes that occur in the brain during sleep. Bremer's early transection studies identified the brainstem as a critical region for control of sleep and conscious state (Baghdoyan, 2002), and subsequent work by Jouvet amongst others identified serotonin and noradrenalin as essential neurotransmitters in the regulation of the sleep-wake cycle (Jouvet, 1969). The development of microelectrode and microdialysis technologies led to significant progress in this field, and other neurotransmitters involved in this process were subsequently identified, including acetylcholine, histamine, dopamine, and GABA. The 'reciprocal interaction hypothesis' was proposed by Hobson in 1975 to describe the relationships between these neurotransmitters during the sleep-wake cycle (Hobson, 1975), and remains widely accepted today. However, almost all data on the neurochemical changes in sleep are based on animal studies, as methodological limitations have hampered attempts to investigate this area in the human brain to date.

1e. Frontal lobe epilepsy and its relationship to sleep

These scientific discoveries, among others, resulted in major advances in the understanding of physiological and pathophysiological aspects of sleep and epilepsy. In the field of epilepsy, characteristic electroclinical patterns were delineated for both generalised and partial epilepsies. Characteristic frontal lobe seizure patterns, such as supplementary motor area (SMA) seizures, were recognised through the intraoperative electrical stimulation studies of Wilder Penfield and colleagues in the 1940's and 1950's (Penfield, 1951, 1954), in conjunction with the clinical studies of Ajmone-Marsan (Ajmone-Marsan and Ralston, 1957). However, the full spectrum of seizures seen in frontal lobe

epilepsy (FLE) was not fully appreciated for considerably longer. This was due in part to the bizarre and unusual semiology often seen with FLE, but also largely because many frontal lobe seizures are not associated with ictal changes on scalp EEG. Frontal lobe seizures were often confused with pseudoseizures when occurring in wakefulness, and with parasomnias in sleep. Lennox and Lennox recognised "running fits" which they considered to be a rare form of epileptic seizure, difficult to distinguish from a parasomnia. This led them to remark that "The unconsciousness of an epileptic seizure is a mystery which is compounded when it is combined with the unconsciousness of sleep" (Lennox, 1960).

The particular relationship between sleep and frontal lobe epilepsy began to emerge with the development of video EEG monitoring. In 1981 Lugaresi and Cirignotta described 5 patients with nocturnal episodes characterised by limb posturing and dyskinetic movements which were brief but occurred many times per night (Lugaresi and Cirignotta, 1981). These episodes were not associated with interical or ictal EEG abnormalities and occurred exclusively in stage 2 of sleep, leading the authors to suggest that this was a new form of movement disorder which they called Nocturnal Paroxysmal Dystonia (NPD). However, evidence soon started to accumulate indicating an epileptic basis to NPD (Meierkord et al., 1992). Increased recognition of the spectrum of frontal lobe seizure semiology (Williamson et al., 1985), in conjunction with placement of additional zygomatic and sphenoidal electrodes in some NPD patients (Tinuper et al., 1990), established that NPD was in fact a form of frontal lobe epilepsy, which was subsequently termed nocturnal frontal lobe epilepsy (NFLE). The phenotype of NFLE has subsequently been well described (Provini et al., 1999), and a number of features have been identified that allow the differentiation of NFLE from parasomnias (Zucconi and Ferini-Strambi, 2000). The importance of formal video EEG monitoring in diagnosing these conditions is, however, still widely acknowledged (Provini et al., 2000; Zucconi and Ferini-Strambi, 2000).

More recently it was recognised that NFLE can be inherited as an autosomal dominant condition (Autosomal Dominant Nocturnal Frontal Lobe Epilepsy, ADNFLE) (Scheffer et al., 1994). Mutations have now been identified in the genes coding for the $\alpha 4$ and $\beta 2$ subunits of the $\alpha 4\beta 2$ nicotinic acetylcholine

receptor in some families with ADNFLE (Steinlein et al., 1995), but, the majority of affected families do not carry these mutations (Combi et al., 2004) suggesting that ADNFLE is a clinically and genetically heterogeneous disorder.

While there has been enormous progress in the understanding of frontal lobe epilepsy and its relationship to sleep, there remain many areas of this relationship which are poorly understood. These range from the underlying neurochemical changes of sleep which apparently precipitate frontal lobe seizures, to clinical difficulties in the diagnosis of paroxysmal sleep-related events, and the full clinical and genetic spectrum of ADNFLE. This thesis is an attempt to address some of these aspects.

CHAPTER 2

THE NEUROBIOLOGY OF SLEEP

Introduction

Although sleep has fascinated philosophers and writers for millennia, modern scientific study in this area dates back only 40 or 50 years. During this time our understanding of the physiological processes underlying sleep has advanced considerably through both animal studies and human research, the latter having been greatly facilitated by the development of polysomnography (PSG). This technique, which allows the monitoring of various physiological parameters in the sleeping subject, is now the principal technology used in sleep medicine. In this chapter I will review the basic phenomena of normal sleep, and the associated physiological changes as measured by polysomnography. I will then discuss the neurochemical processes which are responsible for the regulation of sleep stages, as well as the chronobiological mechanisms which influence them, before going on to describe their neurophysiological consequences. Finally, I will briefly discuss some of the theories relating to one of biology's greatest unsolved mysteries: the function of sleep.

Section 2.1. Sleep: basic phenomena

Sleep is usually defined as a reversible behavioural state of perceptual disengagement from, and unresponsiveness to, the environment (Carskadon, 2004). For centuries it was considered to be a passive state, in which the brain was 'turned off', and essentially characterised only by an absence of wakefulness. While this concept, summarised in the ancient Greek proverb 'sleep and death are brothers', existed for millennia, it is now recognized that sleep is in fact an active, complex, and highly regulated process.

2.1a. The Stages of Sleep

Three distinct states of consciousness are recognized in humans and most animals: wakefulness, non rapid eye movement (NREM) sleep, and rapid eye movement

(REM) sleep. These are defined according to established polysomnographic criteria (Rechstaffen, 1968), and are based on electroencephalographic and other physiological parameters.

Wakefulness. The EEG of adults in relaxed wakefulness with eyes closed is characterized by posterior rhythmic alpha activity. This pattern is attenuated by eye opening or attention, when the EEG shows a low voltage, mixed frequency 'activated' or 'desynchronized' pattern.

NREM sleep. NREM sleep is subdivided into four stages (stages 1 to 4) which reflect the 'depth' of NREM sleep and are characterized by increasing synchronization of the EEG. In stages 1 and 2 (often referred to as 'light' sleep), increasing background theta activity is seen on the EEG, along with sleep transients such as vertex waves, sleep spindles and K complexes. In stages 3 and 4 (often referred to as 'slow wave sleep'), increasing amounts of high amplitude delta activity are seen; sleep transients such as spindles are seen less frequently in these stages. The stages of NREM sleep are defined distinctly on polysomnographic criteria, but in fact represent a continuum of a single process. During the progression though NREM stages 1 to 4, arousal thresholds increase corresponding to 'deeper' sleep (Williams et al., 1964). The metabolic rate of the brain decreases, such that in slow wave sleep it is about 70% of normal waking levels (Maquet et al., 1992; Maquet, 1995). EMG tone gradually declines in NREM sleep, although is not lost completely and limb movements remain possible (Chase, 2004). The metabolic rate of the body as a whole reduces by 5 - 17% (White et al., 1985; Ryan et al., 1989), and physiological changes consistent with this reduced metabolic activity (with functional prevalence of parasympathetic influences) are observed. Heart rate and blood pressure are reduced and stabilized (Coccagna et al., 1971); ventilation, although somewhat unstable during light sleep (Trinder et al., 1992), decreases and becomes highly stable in slow wave sleep with reduced rate but a slight increase in tidal volume (Birchfield et al., 1959). Thermoregulatory function is maintained in a fashion similar to that in quiet wakefulness (Glotzbach and Heller, 1976), although body temperature is downregulated (Parmeggiani et al., 1971). Overall, NREM sleep is

conceptualized as a regulating but relatively inactive brain in a resting but movable body.

REM sleep. In contrast to NREM sleep, the EEG during REM sleep is characterized by activation and 'desynchronisation', such that it resembles the patterns seen in wakefulness. This is accompanied by muscle atonia (resulting from brainstem-mediated inhibition of spinal motoneurons) and bursts of rapid eye movements. While REM sleep is not usually subdivided in clinical practice, physiologically it is recognized that there are two forms of REM sleep. 'Tonic' REM sleep (when the eyes are still) has physiological features which are present throughout the REM sleep period; phasic REM sleep, on the other hand, is characterised by episodic physiological changes which accompany rapid eye movements. In both tonic and phasic REM, muscle atonia is accompanied by a cessation of thermoregulation (Glotzbach and Heller, 1976), such that body temperature drifts towards environmental temperature (Glotzbach and Heller, 1976). During phasic REM, marked irregularities of heart rate, blood pressure and respiratory rate are seen at this time, in contrast to the marked regulation of NREM sleep (Birchfield et al., 1959; Coccagna et al., 1971). The phasic features of REM sleep appear to be generated by ponto-geniculo-occipital (PGO) spikes, which are high amplitude potentials, originating in the pons and propagating to the lateral geniculate nucleus and on to the occipital cortex and the nuclei of extraocular muscles (Morrison and Bowker, 1975). They are not usually visible in humans, but have been widely studied in feline sleep. The cerebral metabolic rate in REM sleep, as measured using FDG-PET, is significantly greater than in NREM and is comparable to that during wakefulness (Maquet, 1995; Maquet et al., 1996). Overall, REM sleep is conceptualized as a highly active brain in a paralysed body.

2.1b. Sleep architecture

The stages of NREM and REM sleep do not occur randomly, but alternate throughout the night with a distinct pattern and structure known as the sleep architecture (Figure 2.1). Sleep is entered through NREM sleep, and REM sleep does not occur until 80 minutes or more of NREM. NREM and REM sleep then

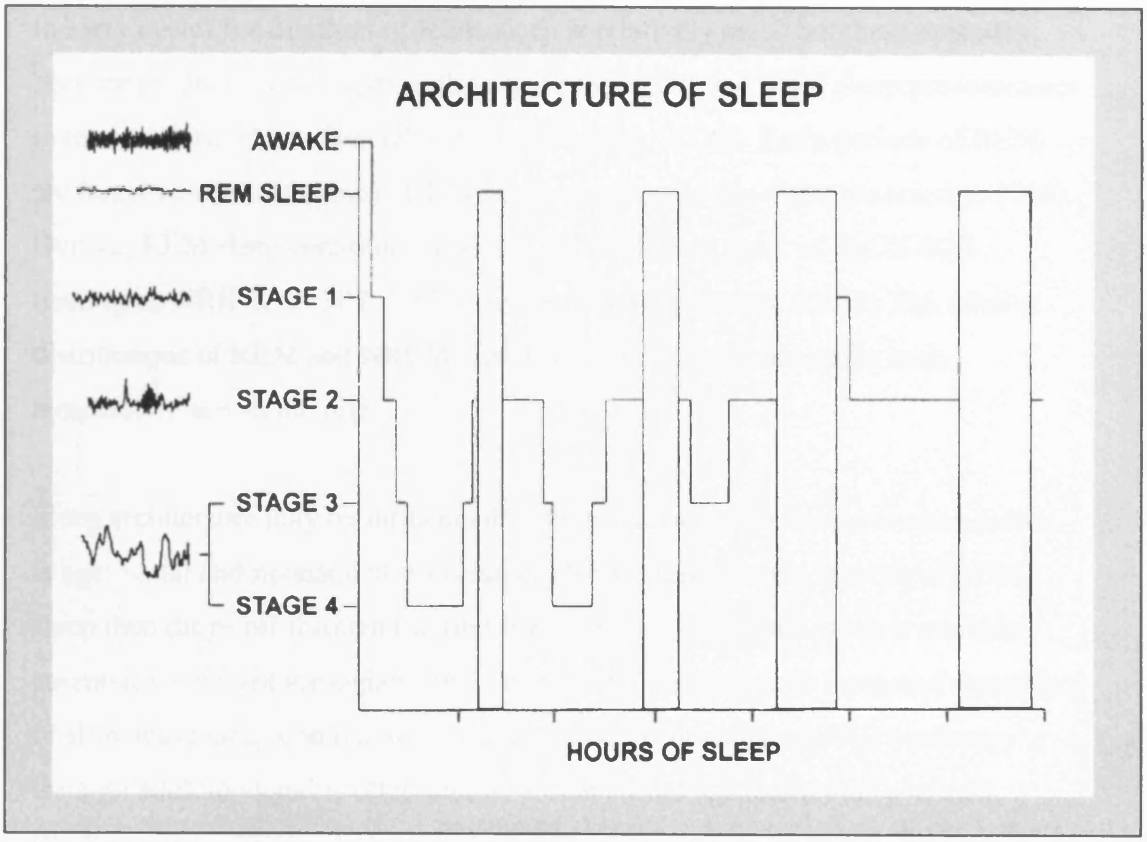


Figure 2. 1. *Hypnogram of normal sleep architecture in a young adult. Normal sleep follows a well-organised pattern, with cycles of NREM and REM sleep; the longest periods of NREM sleep are in the early cycles, wheras REM sleep predominates in the later cycles in the sleep period. Typical EEG patterns (on a PSG timescale) are shown on the left. From Culebras, A (Ed). Handbook of Clinical Neurology. Boston, Butterworth-Heinemann, 1996, p35.*

alternate throughout the night; the cycle has a period of around 90 minutes, with typically 4 to 6 cycles per night. Slow wave sleep (stage 3 and 4 NREM sleep) predominates in the first third of the night, but occupies less time as the night progresses. Later periods of NREM sleep are largely composed of stage 2 sleep. In early cycles the duration of REM sleep is relatively brief, but these episodes become progressively longer as the night progresses, and REM sleep predominates in the last third of the night (Zeman and Reading, 2005). Early periods of REM are largely tonic, with phasic REM being seen later in the night (Aserinsky, 1969). Overall, REM sleep constitutes about 20-25% of sleep time; of the 75-80% making up NREM, 15-30% is slow wave sleep (Carskadon, 2004). The relative distributions of REM and NREM appear to be related to changes in body temperature across the night.

Sleep architecture may be influenced by many factors. The most common factor is age; foetal and neonatal sleep is largely REM sleep, but the amount of REM sleep then drops off through the first few months of life, from when it remains essentially constant throughout life. Infants and children have increased quantities of slow wave sleep compared to young adults; the quantity of SWS declines through adulthood and is often almost absent by old age, particularly in men (Redline et al., 2004), when arousals become increasingly frequent. Temperature, circadian rhythm disturbances (such as jet-lag), drugs and disease (both primary sleep disorders and numerous neurological and other medical conditions) may all disrupt the normal sleep architecture (Carskadon, 2004).

2.1c. Dreaming

The association of dreams and mental activity with different sleep states has been largely deduced from sleep laboratory studies, in which subjects are woken from different sleep stages and asked to describe any dream imagery present at the time. An early and robust finding from such studies was the now widely-known association between REM sleep and dreaming (Dement and Kleitman, 1957). However, subsequent studies have confirmed that around 80% of wakings from REM sleep are associated with dream recall, they have also demonstrated that 25-50% of wakings from NREM sleep are associated with dream reports (Foulkes,

1962; Nielsen, 2000). Dream recollections from REM sleep are longer, more vivid, emotional, and dramatic, and have a more bizarre quality than NREM dream reports, which are typically brief, thought-like and mundane (Hobson et al., 2000). There is some debate as to whether the same processes are at work in these states or whether NREM and REM dreams are in fact produced by different cerebral mechanisms; it is also possible that apparently NREM-associated dreams are remembered from prior REM periods. Some researchers have proposed that brief periods of 'covert' REM sleep (which are too brief to reach PSG staging criteria) within NREM sleep may be responsible for NREM dreaming (Nielsen, 2000). So while dreams are most strongly associated with REM sleep, the role of NREM sleep in dreams is less clear and remains a source of some controversy.

Section 2.2. The neurochemical basis of sleep

While the physiological changes of sleep can be measured in humans using polysomnography, the neurochemical mechanisms underpinning them have been established through alternative methods, principally animal studies. Sleep-wake state is regulated through a variety of neurochemically distinct neural systems, the nuclei of which are located in the brainstem, diencephalon and basal forebrain. There is considerable interaction between these systems, and most send extensive projections throughout the brain through which they exert diffuse modulatory effects on brain function (Figure 2.2). The sleep-wake state of the organism ultimately depends on the balance and interplay of these distinct but highly interconnected systems. In this section I will describe each system individually before going on to discuss the interactions involved in the regulation of sleep and wakefulness.

2.2a. Neurotransmitters involved in the regulation of sleep

Glutamate. Glutamate is the major stimulatory neurotransmitter in the brain and has a key role in the maintenance of wakefulness (Jones, 2003); glutamate antagonists, such as ketamine, have sedative or anaethetic properties (Mayer and Westbrook, 1987). Glutamate is found in high concentrations in the brainstem reticular formation, a loose collection of neurons extending from the caudal

medulla to the midbrain. The reticular formation receives inputs from a wide number of sensory systems and sends excitatory projections to subcortical structures, particularly the intralaminar and midline thalamic nuclei. These excitatory projections play a critical role in thalamocortical activation, which produces the 'desynchronized', low amplitude EEG pattern seen in wakefulness (Steriade, 2005).

Gamma-Aminobutyric Acid (GABA). GABA, the major inhibitory neurotransmitter in the brain, also plays an important role in the regulation of sleep; drugs which enhance GABAergic transmission, such as benzodiazepines, have sedative properties. GABAergic neurons are distributed throughout the brainstem and basal forebrain. Within the reticular formation, they appear to inhibit the excitatory glutamatergic neurons (Jones, 1995). In the thalamic reticular nucleus, which plays a key role in the generation of sleep spindles, GABA-mediated inhibition appears to be a fundamental prerequisite of slow wave sleep and the cortical deafferentation that accompanies it (Steriade, 2004). In the ventrolateral preoptic area of the hypothalamus (VLPO), GABA-containing neurons send inhibitory projections to the tubomammilary nucleus (histamine), dorsal raphe nuclei (serotonin) and locus coeruleus (norepinephrine) (Sherin et al., 1998). Release of GABA in these regions is lowest in wakefulness, intermediate during NREM sleep, and highest in REM sleep; it therefore seems likely that GABA release from the VLPO area is directly involved in the modulation of sleep through effects on the NOR, histamine and 5-HT systems (Nitz and Siegel, 1997; Nitz and Siegel, 1997).

Serotonin (5-hydroxytryptophan, 5-HT). The serotonergic system is comprised of several neuronal groups, the somas of which form dorsal and median raphe nuclei (RN). These nuclei are located in a medial saggital plane extending from the medulla to the midbrain, and give rise to extensive efferent projections which extend to all areas of the brain, as represented in Figure 2.2 (Azmitia and Segal, 1978). Serotonin is implicated in the modulation of a wide range of behavioural functions including the sleep-wake cycle, affect, cognition and motor function (Veasey et al., 1995; Fornal et al., 1996; Meneses, 1999; Ursin, 2002). This diversity of functional effects is not a function of RN firing patterns, which are

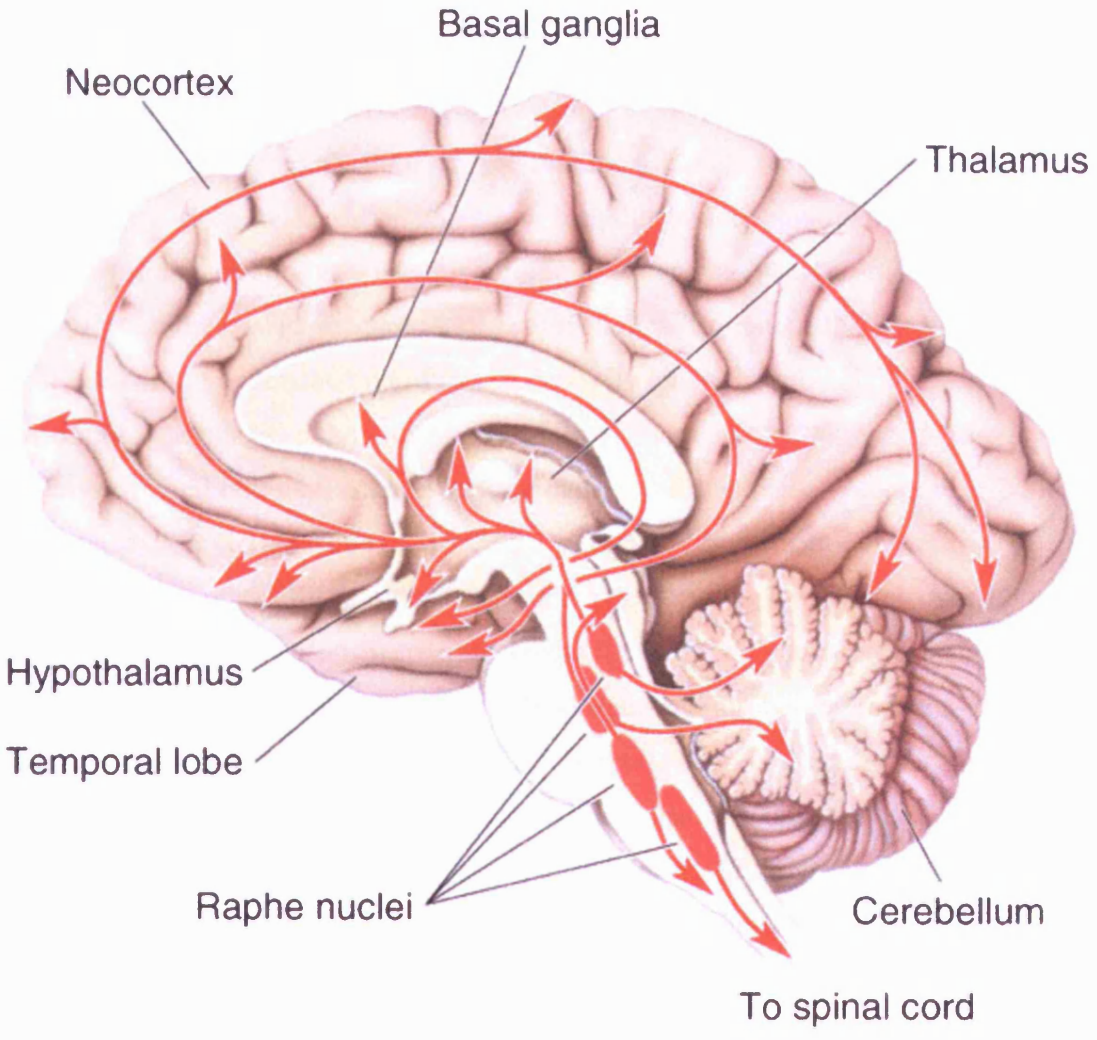


Figure 2. 2 *Schematic representation of the nuclei and projections of the serotonergic system. Although serotonergic nuclei are located almost exclusively in the raphe nuclei in the brainstem, they send projections to almost all regions of the CNS.*

simple and reflect their ancient phylogenetic roots (Peroutka and Howell, 1994), but result from the large number of serotonergic receptor subtypes which have different structural and operational characteristics (Hoyer et al., 2002). The sleep-wake effects of serotonin appear to be mediated primarily through $5HT_{1A}$ receptors (Bjorvatn and Ursin, 1998), which are distributed widely throughout the central nervous system (Hoyer et al., 2002); 5-HT binding to $5HT_{1A}$ receptors may occur at the synapse, or on more distant receptors (including autoreceptors) in a 'non-synaptic' fashion. Although a role for serotonin in sleep has been postulated for many years on the basis brain stem transection studies (Bremer, 1937; Jouvet, 1967), the current understanding of its role has only emerged through technological advances in the last three decades. Landmark electrophysiological studies performed in intact, unanaesthetised cats established that serotonergic neurons had clear state-dependant discharge patterns. When electrodes were positioned to record the discharge patterns of single dorsal raphe neurons over a seven day period, the neurons were observed to fire at their highest rate during wakefulness, with rates slowing during NREM sleep and discharges ceasing completely during REM sleep (McGinty and Harper, 1976; Trulson and Jacobs, 1979). Subsequent microdialysis studies confirmed that serotonin release in forebrain areas is highest in wakefulness, reduced during NREM sleep and lowest in REM sleep, thus paralleling the single cell discharge patterns (Wilkinson et al., 1991; Portas and McCarley, 1994; Portas et al., 1998; Strecker et al., 1999). In addition to these findings, systemic administration of $5\text{-}HT_{1A}$ agonists (such as 8-OH-DPAT) and selective serotonin reuptake inhibitors (SSRIs, such as fluoxetine) increase wakefulness and reduce REM sleep (Sharpley et al., 1996; Bjorvatn et al., 1997). Taken together, this evidence indicates that serotonin promotes wakefulness and inhibits REM sleep; these are commonly referred to as 'REM-off' properties.

Norepinephrine (noradrenaline, NOR). Norepinephrine-synthesising neurons are located principally in the locus coeruleus (LC) which lies in the dorsorostral pons. Like serotoninergic neurons, these send diffuse projections to the cortex and other regions including hippocampus, thalamus and hypothalamus (Foote et al., 1983). NOR appears to have 'REM-off' effects on the sleep-wake cycle, similar to those of serotonin, and the neurons of the locus coeruleus display similar firing

properties to those of the raphe nuclei (Hobson et al., 1975; Aston-Jones and Bloom, 1981). In other words, they are active during wakefulness, less active during NREM sleep and quiescent during REM (Foote, 1980; Aston-Jones, 1981). Furthermore, stimulation of the norepinephrinergic system promotes wakefulness and EEG activation (Berridge and Foote, 1991; Cape and Jones, 1998) wheras inhibition of the system leads to a reduction in fast activity and arousal patterns on EEG (Berridge et al., 1993). While NOR, in concert with 5-HT, plays an integral role in the initiation and maintenance of wakefulness, it appears to have some specific properties. There is evidence that NOR promotes enhanced attention to important stimuli, and may therefore have a role in maintaining wakefulness in stressful or interesting situations (Jones, 1991; Berridge and Waterhouse, 2003); for example, NOR deficient mice have been shown to have normal sleep-wake patterns, but fall asleep more quickly than normal mice after periods of mild stress (Hunsley and Palmiter, 2003).

Histamine (HA). Histaminergic neurons are located exclusively in the tubomammilary nucleus in the posterior hypothalamus and project to practically all brain regions (Brown et al., 2001). Like NOR and 5-HT - releasing neurons, they have a 'REM-off' firing pattern (highest in wakefulness, lower in NREM sleep and very low in REM sleep) and appear to promote wakefulness (Steininger et al., 1999). Pharmacological studies provide further evidence for the wake-promoting properties of histamine, with administration of histamine H_1 receptor antagonists resulting in increases in both REM and non-REM sleep in experimental settings (Monti et al., 1986; Lin et al., 1988), and reducing sleep latency in clinical practice (Roehrs et al., 1984). Histamine H_1 receptor agonists have the opposite effect, increasing wakefulness and reducing REM and NREM sleep (Monti et al., 1986). Findings in histamine-deficient mice suggest that HA may be particularly important in the initiation of wakefulness from sleep, as well as the maintenance of wakefulness in potentially soporific situations (Parmentier et al., 2002).

Dopamine. Dopamine is the most abundant monoamine in the brain, and is organized into three main systems: the nigrostriatal, mesocorticolimbic and tuberoinfundibular systems. While its effects on movement, motivation and

reward are well recognized, its role in sleep is less clear (Rye, 2004). There is evidence that dopamine promotes wakefulness, but the mechanisms by which it does so are not well understood. For example, dopamine agonists clinically tend to promote wakefulness, wheras antagonists increase sleepiness and sleep (Nicholson and Pascoe, 1990). Most individuals with Parkinson's disease complain of disordered sleep (Clarenbach, 2000), and the link between Parkinson's disease and REM sleep behaviour disorder has suggested a role of dopamine in the regulation of REM sleep. Furthermore, the stimulants amphetamine and methylphenidate appear to exert their effects largely or exclusively through effect on the dompaminergic system (Kuczenski and Segal, 1997, 2001). Despite these findings, however, experimental studies of dopaminergic neuronal firing rates and extracellular dopamine concentration (measured by microdialysis) have demonstrated no change in either parameter across the sleep-wake cycle (Miller et al., 1983; Shouse et al., 2000). So, while it is widely accepted that dopamine can promote arousal, further work is needed to clarify the mechanisms by which it does so.

Acetylcholine (ACh). Cholinergic neurons are located in two main regions in the central nervous system which project to different regions. Firstly, the pedunculopontine (PPT) and laterodorsal tegmental (LDT) nuclei, located in the pons, send projections to the pontine reticular formation, the basal forebrain, the thalamus (particularly the midline and intralaminar thalamic nuclei) and the hypothalamus (Armstrong et al., 1983; Steriade et al., 1988). Secondly, a group of cholinergic nuclei is located in the basal forebrain (nucleus basalis, substantia innominata, nuclei of the diagonal band, and septum), and these send widespread projections to the hippocampus, amygdale and entire cerebral cortex (Mesulam et al., 1983). During wakefulness and REM sleep, cholinergic neurons in these regions activate thalamocortical signaling, leading to low amplitude desynchronised EEG patterns (Detari and Vanderwolf, 1987; Steriade et al., 1990).

There is considerable evidence to support a fundamental role for acetylcholine in the generation of REM sleep. Cholinergic neurons are active in wakefulness, becoming less active during NREM sleep, but increasingly active again during

REM sleep (Szymusiak et al., 2000; Vazquez and Baghdoyan, 2001). Direct injection of cholinomimetics into the pontine reticular formation produces an REM-like state in animals, an effect which is site dependant and blocked by the muscurinic antagonist atropine (Baghdoyan, 1997). Administration of muscurinic receptor antagonists cause reduced vigilance and EEG slowing (a feature of NREM sleep), as does Alzheimers disease, a condition characterized by loss of cholinergic neurons (Jeong, 2004). Lesions in the PPT/LDT and the basal forebrain nuclei have differing consequences: destruction of the LDT/PPT results in loss of REM sleep, wheras lesions in the basal forebrain result in EEG slowing and reduced vigilance (Stewart et al., 1984; Jones, 2003), implying some independence of function between the regions. It is hypothesized that broad control of sleep-wake state is governed through the PPT/LDT; however, these send extensive projections to the basal forebrain nuclei, through which thalamocortical activation is facilitated, leading to the characteristic EEG appearances in REM sleep and wakefulness (Steriade, 2005).

Hypocretin (Orexin). Hypocretin is a peptide neurotransmitter which was discovered by two groups independently in 1998 (de Lecea et al., 1998; Sakurai et al., 1998). Two forms of hypocretin are recognized, hypocretin 1 and hypocretin 2 (Hcrt-1 and Hcrt-2), which arise from a common precursor, preprohypocretin (Taheri et al., 2002). Hypocretin-producing neurons are located in the dorsal and lateral hypothalamus, particularly in the perifornical area; they project widely throughout the brain but particularly to hypothalamus, amygdala, septum, and monoaminergic centres involved in sleep regulation (including locus coeruleus, raphe nuclei, and tubomamillary nuclei) (Taheri et al., 2002). The importance of hypocretin in the regulation of sleep and wakefulness became apparent with the discovery of a mutation in the hypocretin receptor Hcr-2 gene in a population of narcoleptic dogs (Lin et al., 1999). It was subsequently discovered that about 90% of patients with narcolepsy-cataplexy have undetectable hypocretin levels in their CSF (Nishino et al., 2000), and human postmortem studies of the brains of individuals with narcolepsy show a marked loss of hypocretin neurons (Peyron et al., 2000; Thannickal et al., 2000). The clinical picture of narcolepsy-cataplexy, combined with *in vivo* and *in vitro* studies, have led to the concept of hypocretin as an arousal promoting peptide which stabilizes the awake state.

The major anatomical connections between hypocretin neurons and brainstem monoaminergic centres, combined with *in vitro* studies demonstrating a clear excitatory effect of hypocretin on raphe, locus coeruleus and tubomammilary nuclei, strongly suggest that hypocretin is an excitatory peptide able to act on multiple systems involved in the sleep wake cycle (Sherin et al., 1996; Hagan et al., 1999; Brown et al., 2001; Taheri et al., 2002). Furthermore, hypocretin-producing neurons are active during wakefulness and less active during NREM sleep (Kiyashchenko et al., 2002); CSF hypocretin levels are at their lowest at the end of sleep, increase progressively throughout the awake period, and are highest just prior to sleep onset (Fujiki et al., 2001); and hypocretin levels are increased by sleep deprivation (Yoshida et al., 2001). These properties have led to the suggestion that hypocretin may counteract increasing sleep propensity that builds up during normal wakefulness and sleep deprivation (Nishino, 2003). This would be concordant the clinical picture of hypocretin deficiency in narcolepsy, in which patients are characteristically refreshed by sleep, but after an hour or two awake start to be overcome by irresistible sleepiness (Overeem et al., 2001).

2.2b. NREM, REM and the reciprocal interaction hypothesis

All the systems described above, and probably more, are involved in the regulation of the sleep-wake state. There is no single and discrete 'sleep centre'; rather, behavioural state is determined by interconnections and interactions between these systems.

The *reciprocal interaction model* was first proposed in 1975 to describe the changes in cholinergic and aminergic neurotransmitter system which lead to the alternating patterns of REM and NREM sleep (Hobson et al., 1975). In this model it is proposed that during wakefulness, activity in the reticular activating system (predominantly cholinergic and glutametergic), under the influence of the activity of serotonergic and norepinephrinergic tone, results in thalamocortical activation and the awake state. At this time, specific cholinergic 'REM-on' neurons, also located in the brainstem LDT and PPT are inhibited by projections from the serotonergic and norepinephrinergic 'REM-off' neurons in the LC and RN; these nuclei send serotonergic and norepinephrinergic projections diffusely to the cortex

and elsewhere where they have an activating effect, but also project heavily to the 'REM-on' cholinergic system where they exert a tonic inhibitory influence. As NREM sleep develops, the firing rate of 'REM-off' neurons decreases, leading to increasing thalamocortical hyperpolarisation and the establishment of NREM sleep. As NREM sleep deepens, the 'REM-off" neurons eventually fall silent, at which point cholinergic 'REM-on' neurons are released from inhibition. Activity in these neurons generates the thalamocortical activation and skeletal muscle atonia of REM sleep (Figure 2.3).

The reciprocal interaction model is still held to be essentially correct, with considerable support from experimental evidence (Berridge and Foote, 1991; Portas and McCarley, 1994; Szymusiak et al., 2000). Unsurprisingly, however, it appears to be an oversimplification, with additional intermediate steps and other neurotransmitters involved. For example, it seems that the initial decline in 5-HT and NOR tone in NREM is mediated by GABA release from the VLPO (Nitz and Siegel, 1997), with hypocretin having a contrary effect (Brown et al., 2001). Other neurotransmitters such as histamine have also been shown to be involved in the sleep-wake process, and it is likely that some neurotransmitters (such as hypocretin) have more than one function. Nevertheless, the model appears essentially sound, and remains the basis of the current understanding of the neurochemistry of sleep.

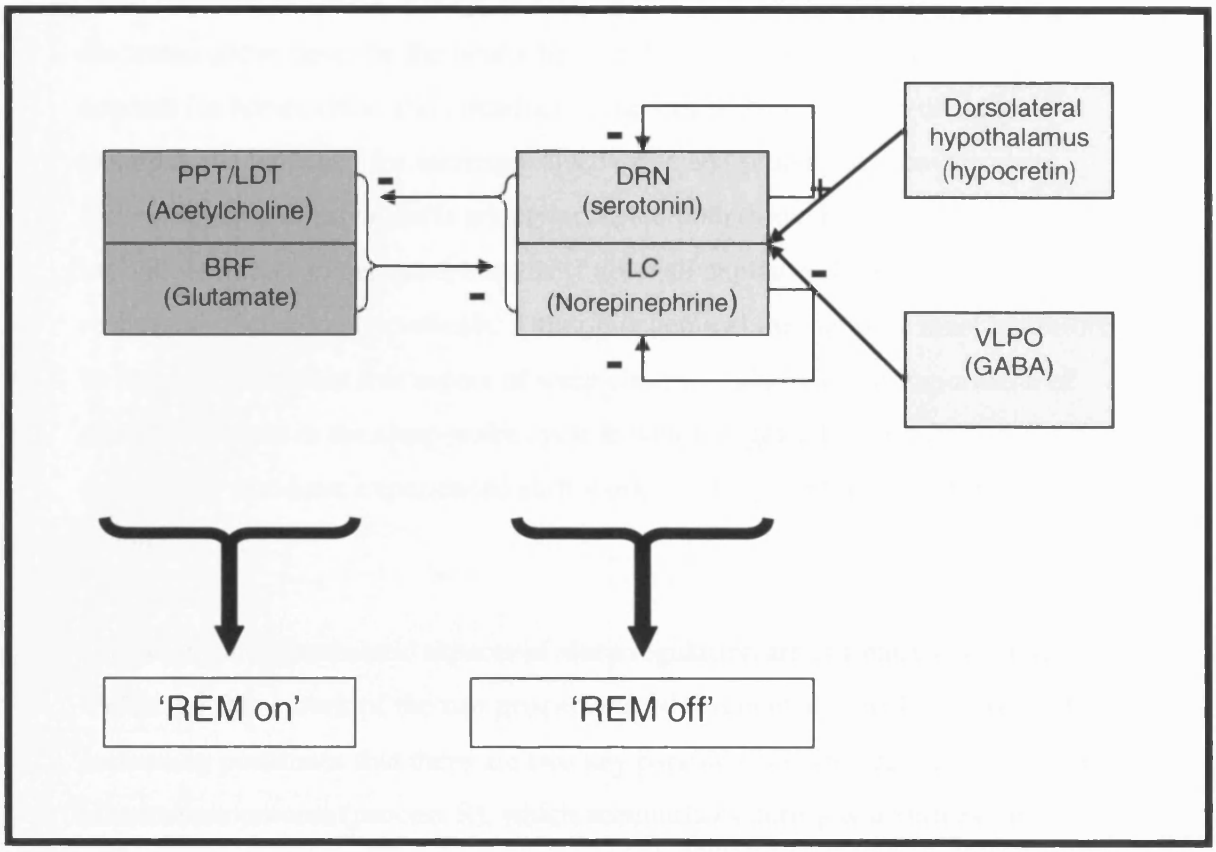


Figure 2. 3 *Summary of the principle neurotransmitter systems involved in sleep regulation. Rapid eye movement (REM) sleep depends on the balance between two mutually antagonistic systems, 'REM on' and 'REM off', which are themselves under the influence of other systems including GABAergic inputs from VLPO and hypocretin from the dorsolateral hypothalamus.*

Abbreviations:VLPO = ventrolateral preoptic area; DRN = dorsal raphe nuclei; LC =locus coeruleus; PPT = pedunculopontine tegmental nucleus; LDT = laterodorsal tegmental nucleus; BRF = brainstem reticular formation

2.2c. Other aspects of sleep regulation: the interaction of homeostatic and circadian processes.

Sleep regulation – the 2 process model. While the neurophysiologic mechanisms discussed above describe the neurochemical basis of sleep regulation, they do not account for homeostatic and circadian influences in the regulation of sleep. For example, the tendency for increased sleep drive and prolonged recovery sleep following sleep deprivation is widely accepted both through scientific study and individual human experience, but this is not well explained by way of the reciprocal interaction hypothesis. Other biochemical mechanisms must, therefore, be invoked to explain this aspect of sleep control. Likewise, the importance of circadian factors in the sleep-wake cycle is well recognized, particularly by individuals who have experienced shift work or jet-lag, and these factors must be accounted for.

Circadian and homeostatic aspects of sleep regulation are currently considered within the framework of the *two process model* (Daan et al., 1984). This model essentially postulates that there are two key parameters in the regulation of sleep: a homeostatic process (process S), which accumulates during wakefulness and dissipates during sleep; and a circadian process (process C), which is determined by endogenous pacemakers and is independent of prior sleep (Figure 2.4). First proposed in 1982, the two process model is still widely accepted and is able to account for a number of recognized phenomena such as jet-lag, the dependence of sleep duration on circadian phase, and recovery after sleep deprivation (Daan et al., 1984).

Process S – the homeostatic process. The term 'sleep homeostasis' refers to the balance of sleep and wakefulness in an individual, and the tendency to counteract deviations from an individual's 'reference level' of sleep (Borbely, 2005). In other words, it refers to those mechanisms controlling the amount of sleep an individual requires, as well as the tendency to become sleepier with prolonged wakefulness and to recoup sleep 'lost' through sleep deprivation.

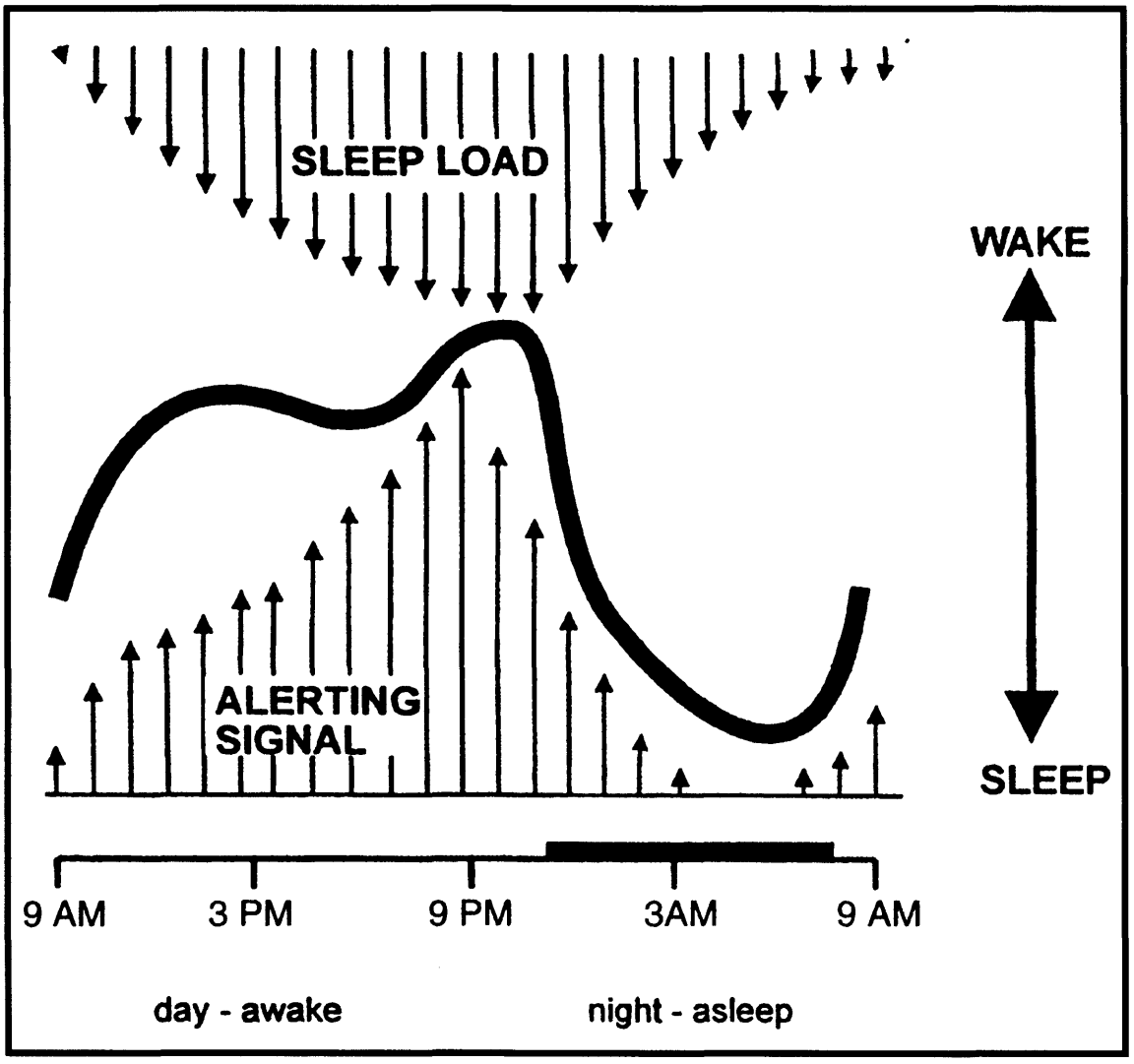


Figure 2. 4 *The two process model of sleep. SCN-dependent alerting promotes wakefulness and opposes sleep 'load', which increases throughout the wake period. When the alerting signal subsides, sleep results. From Shiraki K, Sagawa S, Yousef MK (Eds): Physiological basis of occupational health: stressful environments. Amsterdam: SPB Academic publishing 1996, p253-265.*

The mechanisms involved in this process remain only partially understood, but much interest has focused on the role of somnogens. Somnogens are substances that are said to accumulate in the brain during wakefulness, promoting sleep, and disperse or break down during the subsequent sleep period. In a classic study undertaken in the early 20th century, it was found that injecting the CSF of sleep deprived dogs into the ventricles of non-sleep deprived animals led to rapid sleep onset, a finding that supported the validity of this concept (Legendre, 1913). Since that time, increasing numbers of potential somnogens have been identified, the most widely known and studied being adenosine.

Adenosine (AD), a purine molecule, is released in the brain in response to reduced adenosine triphosphate (ATP) levels. In such situations, which typically result from metabolic stressors such as seizures or ischaemia, AD inhibits neuronal activity and is neuroprotective (Portas et al., 1997). However, sleep deprivation or prolonged wakefulness can also increase AD levels in the basal forebrain and brainstem (Porkka-Heiskanen et al., 1997; Porkka-Heiskanen et al., 2000), with levels falling rapidly during recovery sleep (Arendt, 2004). Direct administration of AD in these regions, particularly the preoptic area, has been shown to promote sleep (Chamberlin et al., 2003; Thakkar et al., 2003), an effect that appears to be mediated via direct inhibition of wake-promoting regions and disinhibition of GABAergic neurons in the VLPO (Thakkar et al., 2003). Moreover caffeine, a methylxanthine A_1 receptor antagonist, has well-known wake promoting effects; and blockade of A_1 receptor synthesis (using an antisense oligonucleotide to the adenosine A_1 receptor mRNA) slightly reduces spontaneous sleep, but strongly reduces rebound sleep following sleep deprivation (de Saint Hilaire-Kafi et al., 1989; Kapas et al., 1993).

In terms of other possible somnogens, the gut peptides insulin, cholecystokinin, and bombesin (Hayaishi and Urade, 2002; Obal and Krueger, 2003), which are released after eating, have been shown to increase slow wave sleep and may be responsible for postprandial sleepiness. Cytokines including interleukin-1β, tumour necrosis factor (TNF) and prostaglandin D_2 (Obal and Krueger, 2003), and hormones including growth hormone releasing hormone (GHRH), growth hormone and prolactin, appear to exert somnogenic effect. A number of other

compounds such as oxidized glutathione and reactive oxygen species are also under investigation as potential somnogens (Moore, 1997).

Process C – the circadian process. In addition to quantitative and homeostatic effects, the effects of circadian rhythm on sleep and wakefulness must also be explained. Circadian rhythms are a feature of almost all eukaryotic organisms (Johnson et al., 1988), and are generated by endogenous biological clocks. They comprise cycles of behaviour and physiology with a period of approximately 24 hours; they occur in the absence of external stimuli but normally are synchronized to environmental day-night stimuli.

The circadian timing system has three main components: *entrainment pathways*, which allow circadian rhythm generators to be synchronized with external stimuli; the *pacemaker*, which generates cyclical output patterns; and *effector systems*, through which the cyclical firing patterns of the pacemakers are translated into physiological and behavioural patterns.

Light is the most important environmental stimulus responsible for entrainment (*Zeitgeber*). The entrainment effects of light are mediated through the retinohypothalamic tract (RHT), essential for this process but unrelated to other visual function (Turek, 1989), which projects directly from the retinal to the suprachiasmatic nucleus (SCN) in the anterior hypothalmus. Locomotor activity is also a zeitgeber (Czeisler et al., 1999), although has weaker effects than light. These stimuli 'entrain' the endogenous pacemaker, the SCN, to environmental stimuli which indicate day or night.

While zeitgebers produce the environmental entrainment of circadian rhythms, the SCN determines the individuals free-running circadian period (τ), which in humans is reported to average 24.2 hours in the absence of light cues (Welsh et al., 1995). The SCN is a population of neurons with intrinsic circadian oscillator properties (Shibata and Moore, 1988), which have extensive interconnections resulting in a distinct pacemaker function; its firing rate is high during the day but low at night (Moore and Danchenko, 2002). The rhythms themselves are generated on a molecular level within the SCN, a process which depends on the

coexpression of specific clock genes, including the *Period* (*Per 1, Per 2,* and *Per 3*), *Cryptochrome* (*Cry1* and *Cry2*), *Clock* and *Bmal1l*. The protein products of these genes interact and oscillate over an approximately 24 hour cycle through a complex negative feedback loop (von Schantz and Archer, 2003). Polymorphisms in these genes may explain variability in sleep propensity and differences in morning or evening alertness between individuals (Moore, 1997).

The outputs of the SCN are not extensive; projections are restricted to the hypothalamus, basal forebrain and midline thalamus (Watts, 1991), although secondary projections exist from these regions to other effector regions in the anterior pituitary and brainstem, thereby mediating control over autonomic and metabolic functions as well as sleep architecture. The SCN also communicates with the pineal gland via a circuitous route, through which it modulates the release of melatonin (Arendt, 2004). Melatonin is effectively a 'darkness hormone', produced at night, and with the duration of secretion reflecting the length of night. Its function appears to be similar in all animals studied, acting as a time signal and organizing daily and annual rhythms; its release is low in daytime and increased at night in both nocturnal and diurnal creatures (von Schantz and Archer, 2003).

The 2 process model – summary. According to the two process model of sleep regulation, sleep timing and structure is regulated by the interaction of homeostatic and circadian processes. This model predicts sleep timing and daytime vigilance, with sleepiness at any given time being a function of both the point in the circadian cycle and duration of prior wakefulness. The model has been validated computationally and has been shown to be sufficient to explain the variability in vigilance and sleepiness during normal wakefulness, as well as the effects of shift work, internal desynchronisation in the absence of time cues, and recovery from sleep deprivation (Daan et al., 1984).

Section 2.3. Electrophysiological changes in sleep

The neurochemical, circadian and homeostatic mechanisms discussed up to this point ultimately exert their influence on sleep and wakefulness through their effects on the intrinsic and synaptic excitability of cortical and thalamic neurons.

These electrophysiogical changes are complex, and a full discussion of the subject is not feasible here. However, it is important to discuss the key electrophysiological correlates of NREM and REM sleep, as well as to briefly review the cellular basis of these features.

2.3a. Electrographic features of sleep

The background EEG patterns in wakefulness and sleep reflect the electrical activity at the cerebral cortex. Individual neuronal potentials are clearly too small to be detectable in scalp EEG, and the millions of action potentials (each lasting about a millisecond) firing almost simultaneously in the cortex simply cancel out. Rather, the EEG detects the rise and fall of summed postsynaptic inhibitory and excitatory potentials, which often occur in parallel in millions of neurons at the same time. Broadly speaking, the EEG patterns of NREM sleep reflect increasing synchronization of neuronal activity in the thalamus and cortex, wheras those of wakefulness and sleep reflect short scale synchronization of fast (20-50 Hz) rhythms over the cerebral cortex resulting in EEG 'activation' or 'desynchronised' patterns.

Features of NREM sleep. The stages of NREM sleep are marked by characteristic EEG changes: attenuation of background rhythms with vertex sharp waves and increasing theta activity mark sleep onset in stage 1; in stage 2, sleep spindles and K-complexes are seen; in stage 3, increasing high amplitude delta activity (0.5 – 3 Hz, anteriorly predominant and greater than 75μV) is seen, occupying 20-50% of the record, and spindle activity is still present during this stage; in stage 4, high amplitude delta activity occupies over 50% of the record, and sleep spindles are only rarely observed (Niedermeyer and Lopes da Silva, 2004).

Features of REM sleep. Electrographically, REM sleep has appearances similar to stage 1 sleep or wakefulness, with a mixed frequency, 'activated' or 'desynchronised' appearance often containing significant theta activity. At times, sawtooth waves are seen over the frontocentral regions, usually in or around phasic REM (Niedermeyer and Lopes da Silva, 2004).

2.3b. Cellular mechanisms of NREM sleep

Experimental studies in animals have shed some light on the neuronal substrates for these EEG changes. The features of NREM sleep seem to broadly arise from three forms of thalamocortical oscillation: spindle oscillations (7-14Hz), delta oscillations (1-4Hz) and slow oscillations (<1Hz) (Steriade et al., 1985; Steriade et al., 1993). Broadly speaking, these NREM features are generated by hyperpolarisation of cortical and thalamic neurons, resulting in increased thalamocortical synchronization.

Spindle oscillations, which are seen as sleep spindles on scalp EEG from NREM stage 2, are seen at relatively low levels of hyperpolarisation and are generated by burst firing in the thalamic reticular nucleus (Steriade, 2004). These oscillations result through rhythmic and repetitive inhibitory bursts in the GABAergic neurons of the thalamic reticular nucleus, which produce rhythmic inhibitory postsynaptic potentials (IPSPs) in thalamocortical neurons. These bursts of inhibition are followed by sychronised postinhibitory rebound excitatory potentials, resulting in characteristic spindle oscillations (Timofeev et al., 1996). In addition to generating spindles, the inhibitory changes in the thalamus are also believed to be responsible for the cortical deafferentation that occurs in NREM sleep (Steriade et al., 1991).

Delta oscillations, responsible for the high amplitude delta of slow wave sleep, also result from inhibitory changes in the thalamic reticular nucleus and thalamocortical neurons. However, these are produced at a significantly greater degree of membrane hyperpolarisation than spindles, and hence the two oscillations are incompatible within a single cell (Steriade et al., 1993); this explains why spindle activity gradually disappears in slow wave sleep. The greater degree of thalamic inhibition at this stage also results in more profound thalamic deafferentation, and hence higher arousal thresholds than in stage 2 sleep.

Slow oscillations are somewhat different to delta and spindle oscillations in that they are generated in the cortex (Steriade, 2004). These oscillations, which have been observed in all major cell classes in the cerebral cortex, consist of slow (0.7-

0.8Hz) hyperpolarisation and depolarisation occurring during both NREM and REM sleep. The main effect of these oscillations is to group and modulate the other patterns seen (e.g. limiting the duration of individual sleep spindles and K complexes). Overall, these three types of oscillation appear to interact during sleep, producing the characteristic scalp EEG patterns of the four stages of NREM sleep (Steriade, 2004).

2.3c. Cellular mechanisms of REM sleep and wakefulness

In contrast to NREM sleep, the EEG in wakefulness and REM sleep is characterised by low amplitude, mixed (but high) frequency activity. This pattern, reflecting activation of thalamocortical networks, is controlled by cholinergic inputs to the thalamus. In essence, these inputs have two major effects: they enhance thalamocortical excitability; and they inhibit the activity of the thalamic reticular nuclei, responsible for the generation of spindles and delta activity, the features of NREM sleep (Pare et al., 1988; Steriade et al., 1988).

The majority of thalamic inputs from the brainstem reticular formation act on association thalamic nuclei; the neurotransmitters involved are not known (although are probably largely glutamatergic). However, there are also major brainstem projections to the sensory thalamic nuclei; around 90% of these inputs are cholinergic, arising in the pedunculopontine (PPT) or laterodorsal tegmental (LDT) nuclei (Curro Dossi et al., 1991). It has been demonstrated that brainstem cholinergic activity projecting to these thalamic nuclei causes prolonged depolarization of thalamocortical neurons, with a corresponding increase in excitability; cholinergic antagonists in this region block this effect (Steriade and Deschenes, 1988). However, in the thalamic reticular nuclei, the opposite pattern is seen, with cholinergic stimulation producing prolonged hyperpolarisation and inhibiting spindle formation (Hu et al., 1989; Steriade et al., 1996; Steriade et al., 1996). The increased thalamocortical excitability, combined with the inhibition of the reticular nuclei, results in the generation of fast rhythmic activity in intracortical, thalamocortical and intrathalamic networks (Woolf and Butcher, 1986; Steriade, 2004); this produces the low amplitude 'activated' EEG pattern seen in wakefulness and REM sleep. It has been shown that this activated EEG

pattern is, in fact, generated by highly synchronized 20-50Hz gamma activity, and so the term 'desynchronised' is best avoided in this context (Steriade et al., 1996; Steriade et al., 1996).

In addition to the thalamic effects, there is also a direct effect of the cholinergic system on cortical activation in wakefulness and REM sleep. As discussed, while most cholinergic thalamic inputs are to the sensory nuclei, the association nuclei (which have the wide cortical non-cholinergic projections) have inputs from other neurotransmitter systems; cortical activation these nuclei is therefore only indirectly influenced by the cholinergic system. However, direct activation of the cerebral cortex does occur, with cholinergic nuclei in the basal forebrain projecting diffusely and directly to the cortex. These basal forebrain nuclei have extensive connections with the LDT and PPT in the brainstem, and are largely driven by the activity of the brainstem nuclei (Steriade, 2004).

The profound muscle atonia that occurs during REM sleep is also generated via brainstem mechanisms. Clinically this is important as the cerebral motor system is activated during REM sleep; the muscle atonia prevents the physical 'acting out' of dreams during sleep (oneiric behaviours), and failure of this system results in the parasomnia REM sleep behaviour disorder (discussed later). In essence, the brainstem mechanisms which control REM and NREM sleep are also involved in the hypotonia observed. During wakefulness NOR and 5-HT, along with activity of subpopulations of the nucleus pontis oralis (NPO) under the influence of ACh, have an excitatory modulatory effect on pontomedullary motoneurons, thereby facilitating motor function (Chase and Babb, 1973). During NREM sleep, the reduced activity of these systems leads to a reduction in resting tone, observable through EMG monitoring on polysomnography. However, in REM sleep, there is complete dysfacilitation of motoneurons through these mechanisms which, as discussed previously, are silent at this time. In addition, cholinergic 'REM on' neurons, acting via subpopulations in the NPO, excite the inhibitory region of Magoun and Rhines, located in the ventral medulla (Magoun, 1946; Chase, 1976). From here, inhibitory interneurons project to medullary motorneurons where they exert a potent inhibitory effect, causing hyperpolarisation of the neurons through glycine and GABA release (Kodama et al., 2003). This combination of

dysfacilitation and active postsynaptic inhibition results in the muscle atonia of REM sleep.

SECTION 2.4. Sleep Function

The ultimate question with regards to sleep is one of function – why does it happen? Sleep has been found to occur in all animals studied, and yet the reasons for its existence remain unclear. Many theories have been advanced, often based on the consequences sleep deprivation, with most authors proposing different functions for NREM and REM sleep. However, sleep deprivation studies, which have been used widely in both animals and humans to try to understand sleep function, have been unable to provide definitive answers. Total sleep deprivation in rats results in a characteristic pattern with dishevelled appearance, decline in body temperature, weight loss, skin lesions and death in about 14 days (Rechtschaffen et al., 1983). The cause of death has never been definitively established in such cases; certainly there is no evidence of organ failure, and the weight loss is less than that seen in starvation and would net seem sufficient to explain death. In humans, conversely, there is no evidence that sleep deprivation can be fatal. Cognitive, psychiatric and motivational effects are all observed, but interestingly homeostasis and organ function appear essentially unperturbed even by up to eleven days of total sleep deprivation (Bonnet, 2005). However, a 'sleep debt' is incurred, resulting in increased durations of slow wave sleep and, to a lesser extent, REM sleep during periods of recovery sleep (Dijk et al., 1990; Aeschbach et al., 1996).

2.4a. NREM sleep

There are many theories of NREM sleep function, but the most widely quoted fall broadly into three groups. *Restorative* theories view sleep as an opportunity for the brain and body to recover from the stresses and 'wear and tear' of wakefulness (Horne, 1988). This concept is intuitively reasonable in view of the sense of replenishment felt after a good night's sleep. However, there is little evidence that any organ in the body other than the brain undergoes increased repair during sleep; in fact, levels of amino acids in the blood (the major stimulus for tissue repair) are

reduced during sleep as a result of the fasting state. Repair is facilitated by inactivity, but resting wakefulness appears equally or more effective than sleep for this, and there is no evidence that sleep deprivation slows wound healing (Mostaghimi et al., 2005). The release of growth hormone (GH) during NREM sleep has been cited as evidence for such theories, but GH probably has little to do with tissue repair *per se*, although its release may be a mechanism to protect tissue proteins against the effects of the sleep-induced fasting . The significant reductions in cerebral blood flow and metabolic rate observed during NREM sleep do, however, suggest that there may be some restorative function of NREM sleep in the brain (Maquet, 1995; Braun et al., 1997). *Ecological* theories propose that animals remain inactive and out of harm's way during that part of the day-night cycle when they are least equipped to avoid predators and other dangers (during the night for animals that rely primarily on vision, and during the day for those in whom the olfactory sense is dominant (Webb, 1974). However, sleep would seem to be an overly complex physiologic process to evolve where wakeful inactivity would serve the same purpose. In addition, there is a negative correlation between sleep in general and predatory danger, with prey animals having less REM sleep than predators (Allison and Cicchetti, 1976; Berger and Phillips, 1995), making it unlikely to be a biological protection from predatory danger. The third major group of NREM sleep theories relates to *energy conservation* (Berger and Phillips, 1995), based on the similarities between sleep and hibernation (which is generally recognized as a mechanism for reducing energy expenditure during winter). However, recent work has suggested that sleep and hibernation are in fact quite distinct, with periodic arousal and sleep phases within a bout of hibernation suggesting that sleep is necessary even during the hibernating state and may thus serve some other purpose (Kilduff et al., 1993). In addition, the 10% reduction in metabolic rate which occurs during NREM sleep in humans seems insufficient, from an evolutionary perspective, to explain the essential nature of sleep.

2.4b. REM sleep

In contrast to theories of NREM sleep function, REM sleep is often purported to have a role in learning, memory and brain development (Horne, 1988; Stickgold, 2005). Evidence favouring such a role includes ontogenic studies, indicating

particularly high quantities of REM sleep in foetal and infantile development (Ioffe et al., 1980), and studies of learned perceptual skills which usually improve overnight but are disrupted by selective interruption of REM sleep (Karni et al., 1994). However, such studies have numerous methodological problems, and most authors have concluded that a major role for REM sleep in memory consolidation is unproven and unlikely (Siegel, 2001; Vertes, 2004; Stickgold, 2005). The association of REM sleep with dreaming has been a major influence on the development of many theories of REM sleep; however, there is no widespread consensus on the physiological role of dreams or, indeed, whether they have any specific function at all (Horne, 1988).

2.4c. Evolutionary Considerations

NREM and REM sleep patterns, essentially of the same nature as those seen in humans, are present in all birds and mammals, leading many researchers to the conclusion that these sleep states have evolved to serve some vital function. However, an alternative hypothesis has been proposed. In the theory of "advanced wakefulness" it is proposed that REM sleep, with associated loss of endothermic control, is analogous to the primitive resting state of our reptilian ancestors. Reptilian wakefulness, in terms of cerebral function, is said to be equivalent to mammalian sleep, and the "advanced" wakefulness of mammals is the most recent evolutionary development. In other words, according to this model both REM and NREM sleep states are essentially phylogenetic remnants; rather than these sleep states developing to serve a function, it is *wakefulness* has developed. The more primitive resting phases of sleep have been preserved, and taken on restorative or other functions, but are not themselves evolutionary additions (Nicolau et al., 2000).

Conclusion

Sleep is an essential function, ubiquitous in the animal kingdom, but its precise role in life remains unclear. Despite this ongoing mystery, much progress has been made in understanding the mechanisms responsible for its regulation, although many areas of uncertainty remain. Furthermore, many of the insights

into these mechanisms are based on studies in experimental animals; not all findings from animal studies have been replicated in experiments in humans, and there are therefore some risks to directly extrapolating conclusions drawn from animal research to human sleep. With the development of new technologies, however, direct study of the human nervous system in sleep may increasingly become possible.

CHAPTER 3.

IMAGING SLEEP AND SEROTONIN -THE USE OF POSITRON EMISSION TOMOGRAPHY

Introduction

Positron Emission Tomography (PET) is a non-invasive imaging technique which is used to measure specific metabolic, physiological and molecular processes *in vivo*. In essence, the PET scanner works by detecting the rate of accumulation and the distribution of a *tracer* (a specific biologically active compound labeled with a positron emitting radioisotope) in a tissue under study. Many tracers have been developed with properties linking them to specific biologic functions such as glucose utilization, blood flow and receptor binding; as a result, PET has the unique capacity to measure any of these functions *in vivo* in a non-invasive fashion. While this technology may be used to image any region of the body, and can be used in both animal and human studies, this discussion will focus on cerebral PET in humans. In this chapter I will provide an overview of the principles of PET, before discussing principles of receptor binding studies and kinetic modeling. Finally, I will review the use of PET in the study of sleep and, more specifically, evaluate its capacity to examine a key component of sleep regulation, the serotonergic system.

Section 3.1. Principles of Positron Emission Tomography

3.1a. Basic concepts in PET scanning

The fundamental aim of cerebral PET scanning is to detect the rate of accumulation and the distribution of a *tracer*, which is administered intravenously, in the brain. Tracers are labeled with a positron emitting radioisotope (*positron emitter*) such as ^{18}F or ^{11}C. Positron emitters are unstable, neutron-deficient isotopes which achieve stability through the conversion of a proton to a neutron. This conversion, or *decay*, results in the emission of a *positron* (a positive electron, i.e. antimatter) and a neutrino. The positron travels a short distance (up to 2 or 3mm) until it meets an electron; when this occurs, matter meets antimatter

and an *annihilation event* occurs. This releases energy in the form of two photons (of equal energy) which leave the site of the annihilation at 180° to each other. The PET scanner contains an array of scintillation detectors; when an annihilation occurs, photons are detected almost simultaneously on opposite detectors (a *coincidence event*). These coincidence events are registered and recorded by the PET scanner, and the 180° angle also enables tracing of a *line of response (LOR)* of the photons.

Using this data, the source of the annihilation is accurately located and image reconstruction algorithms are used to generate a tomographic image. *Attenuation correction* of the image is an important component of this reconstruction process. It allows for the attenuation by cerebral tissue of photons released in the annihilation, either through photoelectric absorption or scatter, factors of particular concern near the centre of the brain where up to 80% of photon pairs will be lost in this manner (Turkington, 2001). In addition, it should be noted that many photon pairs are lost in the image reconstruction process, as PET scanners are usually constructed with axial rings around the subject's head. As a result, those photons that do not travel in the axial plane (plus or minus about 15 degrees) will not be detected.

Background noise in PET is due in a significant degree to two well recognized but unavoidable phenomena of the scanning process; scatter and randoms. *Scatter* describes the deflection of one or both photons from their original course following the annihilation event; these photons therefore register on the 'wrong' detectors, and the event is thus incorrectly assumed to have occurred on the line joining the two receptors. *Randoms* (random coincidences) occur through photons from two unconnected annihilation events arriving at detectors within the time window used to define a coincidence; as with scatter, an incorrect LOR is generated through such events. Corrections can be made for these phenomena but at the cost of increased background noise (Townsend, 2004).

3.1b. PET Tracers

PET tracers are substances that follow (trace) a biologic process under study (Phelps, 1992). They comprise a pharmaceutical compound or other substrate which fulfils a number of criteria: it should behave in a predictable manner, identical or related to the biologic function being traced; it should be administered in very small quantities compared to the quantity of endogenous compound being traced, such that the tracer's pharmacological properties exert minimal or no effect on the biological system (in general, the dose of tracer should be less than 1% of the mass of endogenous compound); and any difference between the tracer and the natural compound should be negligible (Phelps, 1992). Tracers should have a high *specific activity*, in other words most of the compound should be radioactively labeled, with minimal 'cold' compound present.

The most widely used PET tracers are ^{18}FDG and $H_2{}^{15}O$. ^{18}FDG is used to measure glucose utilization; it is transported into the brain through the blood brain barrier using the same carrier-mediated transport sites as glucose, and is then phosphorylated by hexokinase (as is glucose), when it becomes trapped and accumulates in the cells at a rate proportional to glucose utilisation. $H_2{}^{15}O$ is used to measure regional cerebral blood flow (rCBF). Substantial evidence indicates that excitatory neurotransmission is associated with local increases in rCBF, possibly mediated via nitric oxide release (Northington et al., 1992; Iadecola, 1993). These haemodynamic changes can be detected using $H_2{}^{15}O$, and the technique has been widely used to find areas of brain 'activation' associated with various biological functions or neuropsycholgical tasks (Brooks, 1995; Andersson et al., 1998), although this technique has been largely supplanted by functional MRI.

Although ^{18}FDG and $H_2{}^{15}O$ are well known and widely used, numerous other PET tracers have been developed which are sensitive to a number of more specific processes, such as cellular amino acid uptake (e.g. [^{11}C] methionine) and ischaemic cerebral tissue (e.g. [^{18}F] MISO). Of particular interest in neurology is the use of radioligands which bind to specific neuroreceptors, such as dopaminergic (e.g. [^{11}C] raclopride), cholinergic (e.g. A-85380), benzodiazepine

(11C-flumazenil), and serotoninergic receptors (e.g. [^{11}C] WAY-100635). These ligands are able to measure receptor densities and can often give significant insights into the roles of various neurotransmitter systems in pathological states. However, over the last decade, increasing evidence has accumulated to suggest that the binding of some radioligands (such as raclopride and diprenorphine) may be sensitive to concentrations of endogenous neurotransmitter. Tracers of this type are particularly interesting, as they have the capacity to provide insights into a range of physiological and pathological processes, including human sleep.

3.1c. Quantification of PET using kinetic modeling

In order to obtain information about changes in a particular biological process or function, a paired scan approach is often used. One scan is performed in a 'baseline' state, and a second scan in the same individual performed in an 'activated' state, in which scanning conditions other than the biological function of interest are kept identical. In receptor binding studies using ligands which are sensitive to endogenous neurotransmitter release, the distribution and magnitude of receptor binding between the two scans can provide important biological information regarding the neurotransmitter system under investigation.

While PET scans allow sequential measurements of radioligand distribution over time, the concentration and distribution of the ligand over the time course of a PET scan may be affected by a number of variables besides ligand-receptor binding. Factors such as blood flow, tracer clearance from plasma, specific activity and non-specific binding can vary between the baseline and activation scans, and may have a significant impact on the activity detected by the PET scanner (Ichise et al., 2001). In order to obtain biologically meaningful information, therefore, it is necessary to quantify the data in terms of a measurable parameter of interest. In practice this is achieved by the application of *tracer kinetic models* to the PET data. A full discussion of kinetic modeling is beyond the scope of this thesis, but here I will summarise some of the pertinent details relevant in receptor binding studies.

(i) Parameters of interest. The aim of receptor binding studies is to measure the density of 'available' neuroreceptor sites. The most widely accepted measurement of this function is *Binding Potential* (*BP*) (Mintun et al., 1984), which represents the ratio B_{Max} (the maximum concentration of receptor sites) divided by K_d (the equilibrium dissociation constant of the ligand). In order to estimate BP it is also necessary to measure the *arterial input function,* K_1. Measurement of K_1 usually requires arterial sampling of both the tracer and its radioactive metabolites during the scan, which is an invasive and technically complex process. However, the recent development of reference tissue models (discussed below), have removed the need for arterial sampling in many situations. These models cannot give absolute K_1 values, but are able to generate an estimate of the K_1 ratio between the reference region and the tissue of interest. This ratio, termed R_0, is sufficient to generate BP values and also gives an estimate of relative blood flow between the reference tissue and the tissue of interest.

(ii) Compartmental models. Kinetic models used in PET quantification assume a 'compartmental' system, based upon pharmacological principles, in which a 'compartment' is a volume or space in which the tracer rapidly becomes uniformly distributed (Phelps, 1992). Compartments may have clear anatomical correlates (e.g. intravascular blood volume), but not necessarily (e.g. in brain unbound to receptor is a separate compartment to in brain bound to receptor). Several other assumptions are made in the generation of these models, including: (i) that radioligand in the system comes from a single source, arterial plasma, and that the tracer and plasma are well mixed; (ii) that the system under examination is in a physiological 'steady state' (iii) that radioligand can pass back and forth freely from arterial plasma to the free compartment; (iv) that first-order kinetics can describe the exchange of radioligand between compartments; and (v) that non-specifically bound radioactivity in the second compartment equilibrates rapidly with free tissue radioactivity (Ichise et al., 2001). Movement of tracer between these compartments is assumed to occur in a consistent and predictable fashion through first order kinetics, and is therefore governed by a number of rate constants. Using fundamental mathematical principles and Michaelis-Menton kinetics, first order differential equations are generated which can then be solved to enable measurements of the parameters of interest. In this discussion key

underlying concepts are discussed in the main text, whereas more detailed mathematics is presented in the figures.

A summary of the simplest situation, the two compartment model (used for example with blood flow studies using $H_2{}^{15}O$) is shown in Figure 3.1. Essentially, the measurable parameters here are M_T (the amount of tracer in the tissue of interest, which is measured by PET), and C_A (the arterial concentration of tracer). Sequential measurements of M_T are made over time by the PET scanner (frames), from which a *time-activity curve* can be generated (Figure 3.1b).

C_A is measured (by arterial cannulation) for each of these M_T measurements. Solving of the differential equations in terms of M_T and C_A enables measurement of K_1 (Figure 3.1c), which corresponds to cerebral blood flow.

This basic model cannot be used for ligand studies, however, as the situation is more complex (Figure 3.2); ligand which has entered the brain may either bind to receptors or remain unbound (either free in tissue or nonspecifically bound to other, non-receptor, tissue). This binding must be taken into consideration in the kinetic modeling. Through basic pharmacological principles, the interaction of a free substrate (S) with a free receptor (R) to form the complex RS is described by

$$S + R \leftrightarrow RS$$

The association and dissociation constants (k_{on} and k_{off}) are such that, at equilibrium

$$k_{on}[S][R] = k_{off}[RS]$$

(where [square brackets] represent concentration). The *affinity* (K_d) of a ligand for a receptor is defined as k_{off}/k_{on}, and the total number of receptors is defined as B_{max}, which is [R] + [RS]. So the above equation can be rewritten:

$$[RS] = B_{max}[S]/([S] + K_d)$$

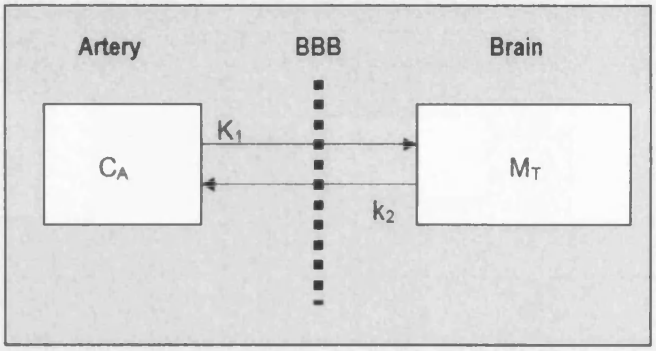


Figure 3.1a .Two compartment model as used for $H_2{}^{15}O$ studies. C_A and M_T represent the concentration of tracer in the plasma (as measured by arterial sampling) and brain (as measured by PET) respectively. K_1 represents the influx rate constant (diffusion from blood to brain), and is equal to the rate of cerebral blood flow; k_2 is the efflux rate constant (diffusion from brain to blood). BBB is the blood brain barrier.

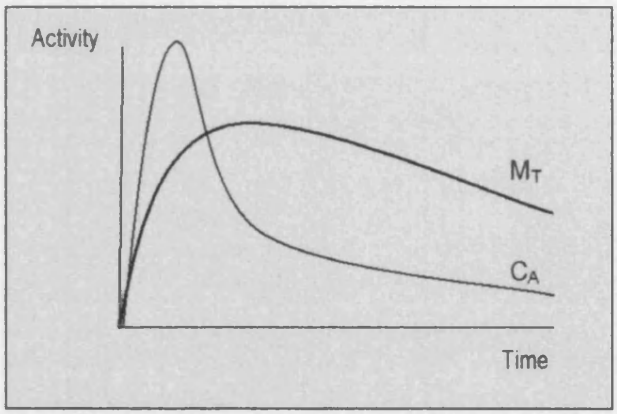


Figure 3.1b. Time-activity curve showing activity in brain detected by the PET scanner (M_T) and tracer in arterial blood (C_A) on the y axis against time on the x axis.

Influx rate = K_1Ca
Efflux rate = $k_2 M_T$

Net rate of accumulation (M_T'):

$M_T'(t) = K_1Ca(t) - k_2 M_T(t)$

The aim is to express K_1 (equivalent to blood flow) in terms of the measurable variables M_T and Ca.

This solves to:

$$e^{k2t} M_T(t) = K_1 \int_0^T e^{k2t} Ca(t)\, dt$$

Figure 3.1c. Summary of mathematical equations used to measure blood flow (K_1).

Figure 3. 1. *Two compartment PET kinetic modeling as used for $H_2{}^{15}O$ studies*

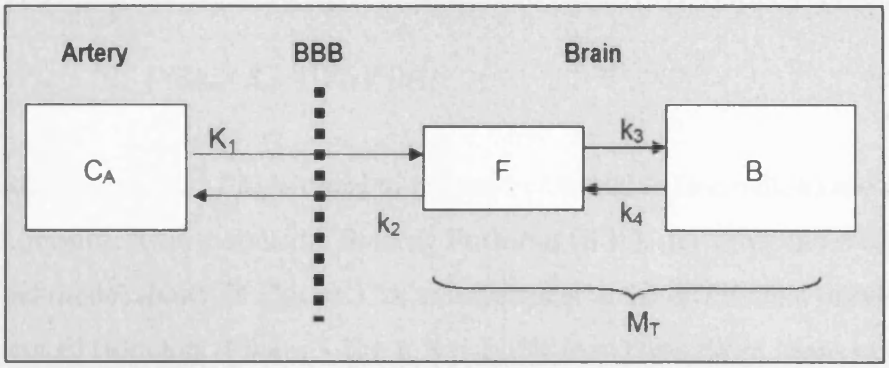


Figure 3.2a. Model for receptor-ligand studies. K_1, k_2, C_A and M_T are defined as in figure 3. F is free or non-specifically bound ligand in brain; B is receptor-bound ligand. k_3 is the association constant (k_{on}) and k_4 is the dissociation constant (k_{off}).

From Fig 3.2a:

$B' = k_3F - k_4B$
$F' = K_1C_A - (k_2 + k_3)F + k_4B$

Where B' and F' are the net rates of accumulation of B and F respectively.

Thus at steady state, where B' and F' = 0:

$k_3 / k_4 = B / F$ = Binding Potential (BP)

AND

$M_T = B + F = K_1 / k_2 \,.\, [k_3 / k_4 + 1]\, C_A$

So:

$M_T / C_A = K_1 / k_2 \,.\, [1 + BP]$

From this point, the equations can be differentiated and solved to give BP in terms of M_T and C_A (final equations not shown).

Figure 3.2b. Summary of mathematical equations used to measure binding potential (BP).

Figure 3.2. *Modeling to determine binding potential (BP) in receptor-ligand studies*

However, in the PET setting, as [S] is a tracer and is hence very small compared to B_{max}, this effectively becomes:

$$B_{max}/ K_d = [RS]/ [S]$$

In other words, B_{max}/ K_d is equal to the ratio of bound to free radioligand at equilibrium. This ratio is the *Binding Potential* (B.P.). By using the receptor-ligand model shown in Figure 3.2a, and rearranging the differential equations generated from this (Figure 3.2b), it is possible to express BP in terms of M_T and C_A, and hence quantify BP in the scan (Figure 3.2b).

(iii) Reference tissue models and model simplification. As discussed previously, a major problem with kinetic modeling used in PET quantification is the need to measure the arterial input function. Such a measurement is essential, and usually requires arterial sampling of both the ligand and its radiolabeled metabolites, an invasive and complex process. However, 'reference tissue' models have been developed for use in ligand studies which allow the use of a reference tissue input function obtained from PET images, removing the need for arterial sampling. Such models require a reference tissue in the brain, in which no specific ligand binding occurs (i.e. a tissue devoid of the receptors being studied). The modeling effectively uses this region as an indirect input function; in other words, differences in binding in this reference region (which by definition will be non-specific, non-receptor related binding) with the binding in the tissue of interest are used to calculate BP values. It assumes that free and non-specifically bound tracer behave in the same manner in reference region and the tissue of interest.

The full reference tissue model (Cunningham et al., 1991) is summarised in Figure 3.3. However, although this method generates robust BP measurements it gives large standard errors for other parameters (Hume et al., 1992). A simplified reference tissue model was subsequently developed by the same group based on a three compartment model, which effectively eliminated this problem (Lammertsma and Hume, 1996); this is summarised in figure 4

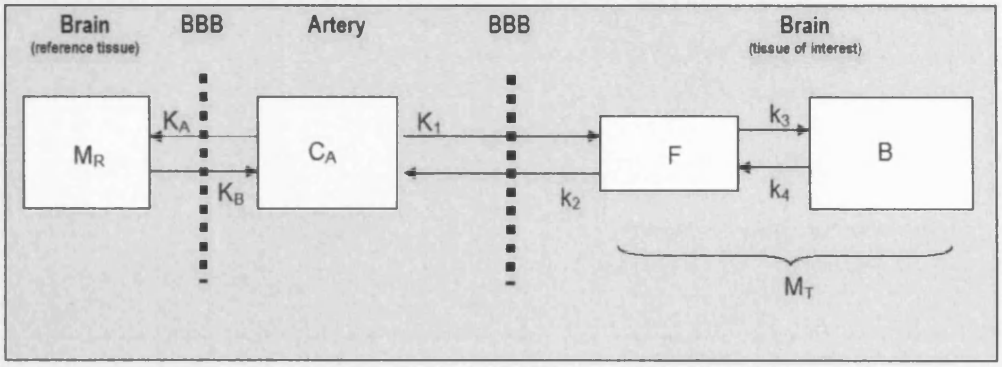


Figure 3.3. Full reference tissue model for receptor-ligand studies. K_1, k_2, C_A, M_T, B, F, BBB are defined as in figure 4. M_R is free or non-specifically bound ligand in reference tissue (by definition this region has no receptor-ligand binding); K_A and K_B are the influx and efflux rate constants for the reference tissue.

The aim of this model is to remove the need for direct measurement of the arterial input (C_A) by using information from the reference region.

So:

$M_R' = K_A C_A - K_B M_R$

Where M_R' is the net rate of accumulation of tracer in the reference tissue. Therefore:

$C_A = M_R' / K_A + K_B M_R / K_A$

So the arterial input function, C_A, is expressed in terms of the accumulation of tracer in the reference region. This form of C_A can be substituted into the equations for the standard receptor-ligand model (Figure 4), removing the requirement for direct arterial sampling.

Figure 3.3. *Full reference tissue model for measurement of binding potential (BP) in receptor-ligand studies withoutthe use of arterial sampling.*

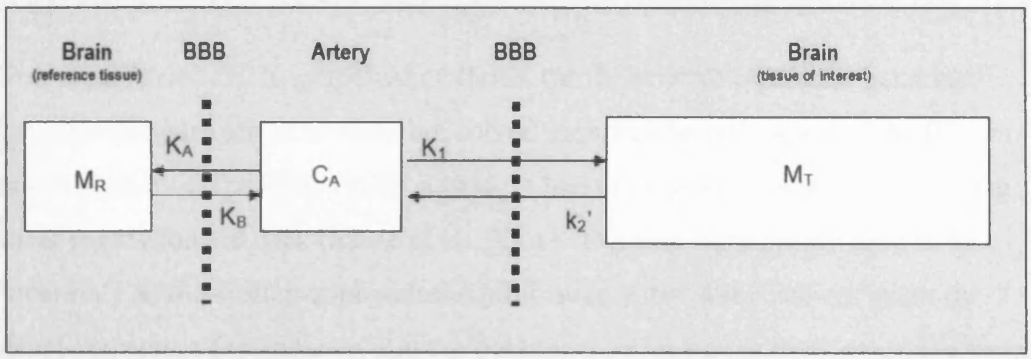
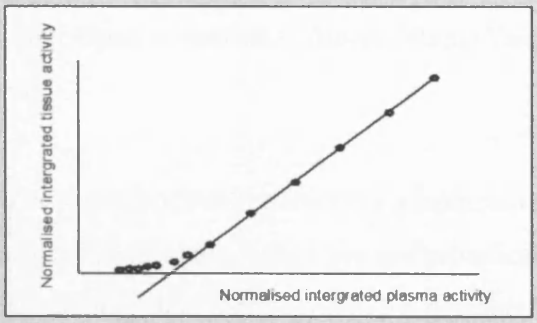


Figure 3.4a. Simplified reference tissue model for receptor-ligand studies. K_1, C_A, M_T, M_R, K_A, K_B are defined as in figure 5. Bound and unbound ligand in the tissue of interest are not distinguished; k_2' is the efflux constant for all tracer in the tissue of interest.

Using this model, it becomes possible through substitution to solve the equations to establish the parameters of interest (including BP and K_1) in terms of M_R and M_T. Overall, this model produces more robust parameter measurements than the full reference tissue model (REFS).

The solution can either be obtained through graphical methods in which BP is obtained from the slope of the linear portion of the (e.g. Logan plot, below);



or non-linear methods, such as the Lammertsma and Hume method which solves to:

$$M_T = K_1/K_A \cdot M_R(t) + k_2[1 - K_1(1+ \mathbf{BP}) / K_A] \int_0^T e^{k'2t(t-T)} M_R$$

Figure 3.4b. Linear and non-linear analysis of simplified reference tissue model

Figure 3. 4. *Simplified reference tissue model for measurement of binding potential (BP) in receptor-ligand studies without arterial sampling*

(iv) ***Graphical vs non-linear analysis methods.*** There are two broad approaches to parameter estimation based on kinetic models.

Graphical Methods. In graphical methods, the differential equations generated from the compartmental models are solved such that an estimation of the BP can be obtained by graphically fitting a straight line to experimental data, or by using linear regression analysis (Ichise et al., 2001). Because such graphs tend to be linear only as the system approaches equilibrium, early points are excluded by visual inspection for linearity, and the parameter of interest is then generated from the linear portion of the graph using linear regression procedures (often linear least squares). Examples of graphical methods include the Gjedde-Patlak plot for tracers with irreversible uptake (Patlak et al., 1983) and the Logan plot for tracers with reversible uptake (Logan, 2000). The Logan plot is useful in ligand studies as it is computationally efficient and can be used with a reference tissue input, removing the requirement for arterial sampling. However, it has been shown that there is some bias inherent in this model, (Slifstein and Laruelle, 2000), although techniques have been developed to minimize this problem (Varga and Szabo, 2002).

Non-linear Methods. These methods differ from the graphical models through the use of non-linear regression techniques, which are mathematically more complex and computationally demanding than those used in the graphical methods. The reference tissue model initially described by Lammertsma and Hume using this approach was based on a four compartment model (Figure 3) and subsequently simplified to a three compartment model (Figure 4) (Lammertsma and Hume, 1996). Despite the computational demands of the simplified reference tissue model, it is robust and has now been validated for use with a number of radioligands (Gunn et al., 1997; Passchier et al., 2001).

In summary, kinetic modeling is an essential process which enables the quantitative estimation of parameters of interest (principally BP in receptor ligand studies) from PET data. These parameters can then be used to look for biologically significant differences between different scans.

3.1d. Using PET to measure neurotransmitter fluctuations in vivo

Over the last 10-15 years there has been significant interest in the measurement of endogenous neurotransmitter flux *in vivo* using PET with neuroreceptor ligands. While many ligands appear insensitive to levels of endogenous neurotransmitter, a number have been identified in whom such sensitivity clearly exists. To date, these have been predominantly D_2 dopamine receptor ligands; the most widely studied is [^{11}C] raclopride. Initial studies demonstrated the sensitivity of [^{11}C] raclopride binding to endogenous dopamine through the use of pharmacological challenges with compounds known to stimulate dopamine release, typically using stimulants such as amphetamine or methylphenidate (Laruelle, 2000). Subsequent studies have gone on to implicate the dopaminergic system in a number of biological processes by demonstrating their association with altered ^{11}C-raclopride binding (Koepp et al., 1998; Laruelle and Huang, 2001).

The conventional explanation for this effect is the classical receptor occupancy model (Seeman et al., 1989). In this model it is proposed that ligands with an affinity for the receptor comparable to that of the endogenous neurotransmitter bind more 'loosely' to the receptor than those with a higher affinity. As a result, these receptors are vulnerable to displacement by increased concentration of endogenous neurotransmitter; their binding is increased in situations of low endogenous neurotransmitter release, but reduced in situations of increased neurotransmitter release (Figure 3.5). However, this model has been increasingly questioned, primarily because affinity is not always a reliable predictor of a ligand's sensitivity to neurotransmitter flux (Laruelle, 2000; Laruelle and Huang, 2001).

A possible alternative mechanism of ligand sensitivity to endogenous neurotransmitter is through receptor internalization or 'trafficking' (Figure 3.6). It is well recognized that many receptors, including D_2 dopamine receptors, are coupled to G-proteins and undergo internalization as a response to agonist stimulation (Dumartin et al., 1998; Martin-Negrier et al., 2000). Internalisation of receptors may differentially affect the binding of a radioligand on the basis of

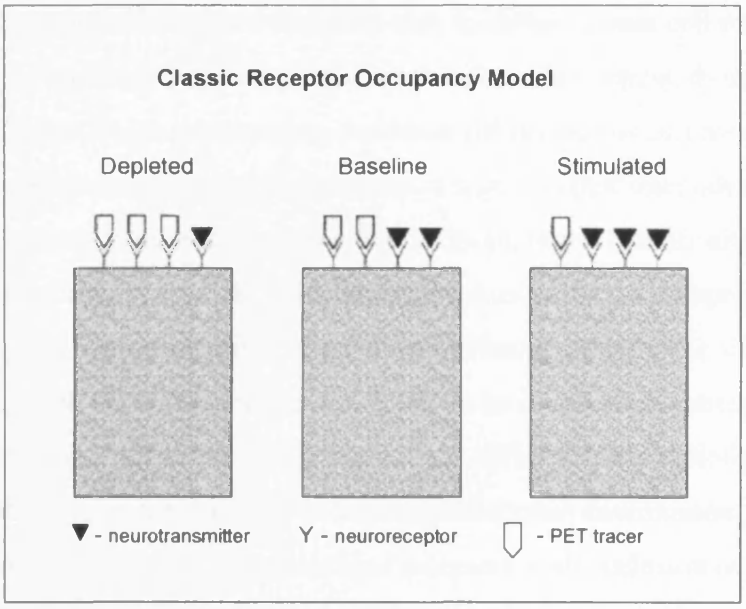


Figure 3. 5. *The classic receptor occupancy model for ligand-neurotransmitter interactions in PET. The radioligand competes directly with endogenous neurotransmitter for receptor binding sites, thereby binding more extensively in situations of reduced neurotransmitter release (Laruelle and Huang, 2001)*

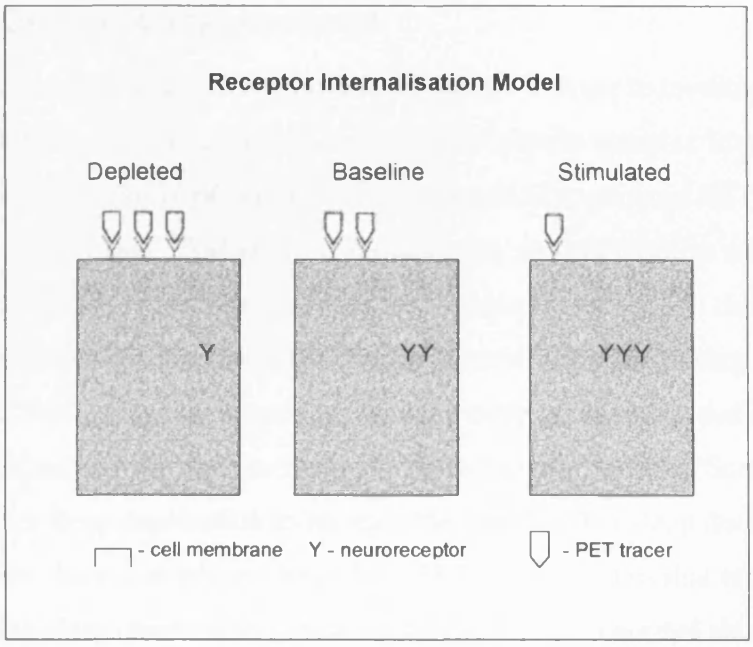


Figure 3. 6. *The receptor internalization (or 'trafficking') model for ligand-neurotransmitter interactions in PET. In situations of increased neuroreceptor internalization (as may occur with increased endogenous neurotransmitter release), neuroreceptors are internalized. In this state they are unavailable for ligand binding, resulting in reduced radioligand binding.*

properties other than affinity, such as lipophilicity. In theory, ligands with high lipophilicity (and which are therefore able to diffuse across cell membranes) should be unaffected by receptor internalization. In contrast, those with low lipophilicity (which are therefore *unable* to diffuse across cell membranes) will have their binding reduced in situations of high receptor internalization (Figure 3.6). Unfortunately, studies indicate that lipophilicity, like affinity, is not necessarily a good predictor of a ligand's vulnerablility to competition from endogenous neurotransmitter (Laruelle and Huang, 2001). The situation is complex, and other factors are also likely to be involved in conferring this property; possibilities include a reduction in affinity of the radioligand for internalised receptors in a low sodium (intracellular) environment, or a conformational change of internalised receptors with occlusion of the binding site for the radioligand (Zimmer et al., 2004).

Section 3.2. The use of PET in sleep studies

3.2a. General considerations.

A number of difficulties confront the researcher looking to investigate sleep using PET. Firstly, PET is a labour-intense and technically complex investigation; as a result, in the majority of centres it is only practical to perform PET scanning during the daytime. Furthermore, the scanning process requires subjects to sleep with their heads immobilized within the scanner, a process that can be uncomfortable. This reduces the chance of obtaining sleep during a scanning session; there is also the possibility that the sleep quality obtained in such a situation may by different to sleep in a more 'normal' setting. Some studies have used prior sleep deprivation to increase the likelihood of sleep during the scan. However, there is ample evidence from EEG-based studies that recovery sleep following sleep deprivation is qualitatively different to normal sleep (Cajochen et al., 1999; Finelli et al., 2001). Moreover, there is substantial evidence that neurochemical changes, particularly in the serotonergic system, result from sleep deprivation (Prevot et al., 1996; Gardner et al., 1997). These issues must be taken into consideration when planning any PET study of sleep.

Most PET studies in sleep have examined either rCBF changes using $H_2{}^{15}O$, or patterns of glucose metabolism using ^{18}FDG. $H_2{}^{15}O$ has some technical advantages which often make this the approach of choice in PET studies of human sleep. $H_2{}^{15}O$ PET requires only brief acquisition times (around 4 minutes), and the tracer has a very short half-life (2.04 minutes). As a result, multiple scans can be performed in different sleep stages during a single sleep period in any given subject. In contrast, ^{18}FDG studies require a long period of data acquisition (30 minutes or more); this factor, combined with the longer half-life of ^{18}FDG which allows only one scanning session in a night of sleep, makes this technique less attractive than $H_2{}^{15}O$. Nevertheless, ^{18}FDG PET has superior spatial resolution in comparison to $H_2{}^{15}O$ PET, an advantage that has been utilized in a number of sleep studies.

3.2b. $H_2{}^{15}O$ Studies.

$H_2{}^{15}O$ studies indicate that, in comparison to wakefulness, NREM sleep results in reduced regional cerebral blood flow (rCBF) in the following areas: central core structures (including brainstem, basal forebrain and thalamus); basal ganglia; cerebellum; and some cortical areas, primarily mesial temporal, frontal and parietal regions (Braun et al., 1997; Hofle et al., 1997; Maquet et al., 1997; Andersson et al., 1998). The reduction in rCBF is most marked and robust in the thalamus. More recent studies have correlated EEG delta power with magnitude of rCBF changes. These demonstrate a decline in rCBF with increasing delta power in similar regions to those identified in the dichotomous NREM sleep/ wake state studies, but with one important difference; correlations between delta power and rCBF are *not* seen in the thalamus and brainstem (Dang-Vu et al., 2005). A study of rCBF on awakening from sleep demonstrated a very rapid increase in rCBF in thalamus and brainstem regions, but a more gradual and progressive increase in rCBF in anterior cortical regions through the first 15 minutes of wakefulness (Balkin et al., 2002).

Taken together, it can be interpreted from these studies that the changes in rCBF (and, by inference, excitatory neurotransmission) seen in the brainstem and thalamus reflect *state-dependent* (i.e NREM sleep versus wakefulness) processes

(Hofle et al., 1997; Dang-Vu et al., 2005). This is concordant with neurophysiological studies of sleep, which indicate fundamentally altered firing patterns in these regions in NREM sleep (see previous chapter for details). On the other hand, the gradual reduction in rCBF in cortical and other regions during NREM sleep indicates a progressive reduction in activity with increasing 'depth' of NREM sleep in these areas (Hofle et al., 1997; Dang-Vu et al., 2005). In combination, these findings support the concept that brainstem and thalamic regions are important in the determination of state (i.e. NREM sleep or wakefulness), whereas cortical function is not only a function of wakefulness or sleep *per se*, but also of depth of sleep and degree of alertness after waking.

REM sleep, in comparison with NREM sleep, is associated with reactivation of central core structures (including brainstem, thalamus, and basal forebrain) as well as the limbic system, and regions responsible for visual and auditory processing (both primary and association cortices); however, frontal and parietal association cortices remain deactivated as in NREM sleep (Maquet et al., 1996; Braun et al., 1997). It has been suggested that this pattern of relative activation seen during REM sleep is consistent with the visually and emotionally rich content of dreams; likewise, relative deactivation of areas responsible for higher order processing may be related to their often bizarre and uncritically experienced nature (Braun et al., 1997).

3.2c. ^{18}FDG studies.

These have been largely concordant with rCBF studies, although with some interesting additional findings. In NREM sleep, a global reduction in glucose metabolism is observed during NREM sleep, which returns to waking levels during REM sleep (Maquet et al., 1990). More specifically, reduction in glucose metabolism is observed in the thalamus and large areas of frontal, parietal, temporal and occipital cortex, primarily in regions of association cortex, with no change seen in limbic and primary sensorimotor areas (Maquet et al., 1992; Nofzinger et al., 2002). However, one study has also shown a clear *increase* in ^{18}FDG uptake in the hippocampus in NREM sleep compared to wakefulness,

potentially supporting the concept that NREM sleep plays a role in memory (Nofzinger et al., 2002).

In REM sleep, global cerebral glucose metabolism resembles that seen in wakefulness (Buchsbaum et al., 1989; Maquet et al., 1990), but may in fact be increased in limbic and paralimbic regions (Nofzinger et al., 1997). These findings are comparable to those from rCBF studies, and appear to give a physical substrate to the rich emotional content widely described in dreams (Stickgold, 2005).

Section 3.3: Serotonin and the CNS

While ^{18}FDG and $H_2{}^{15}O$ PET studies are useful for examining changes in metabolic rate and rCBF during sleep, they provide no information about the behaviour of specific neurotransmitter systems. The serotoninergic system, which appears to play and important role in sleep from animal studies, is a tantalizing target for ligand studies. Besides its role in sleep, this system has a putative role in many other neurological functions, such as cognition, affect, and locomotor activity (Jacobs, 1997), and also in psychiatric and neurodegenerative diseases such as anxiety, depression and schizophrenia (Andrade and Nicoll, 1987; Glennon, 1990; Saxena, 1995). However, while ^{11}C-raclopride and other tracers sensitive to endogenous dopamine release have opened exciting new avenues for imaging dopamine neurotransmission (Koepp et al., 1998), finding comparable ligands for the serotonergic system has proved difficult. Before going on to discuss the current status of serotonergic imaging with PET, however, it is necessary to briefly consider the organisation of this system in the CNS.

3.3a. Anatomy and physiology.

The serotonergic system is composed of several neuronal groups, the somas of which are located in a medial saggital plane extending from the brain stem to the midbrain; these form the *raphe nuclei* (Figure 2.2). These neuronal groups send very widespread projections throughout the central nervous system. The caudal raphe nuclei (magnus, pallidus and obscurus) give rise to a prominent bulbospinal serotoninergic system. The rostral raphe nuclei project, via the medial forebrain

bundle, to extensive forebrain regions including most of the cerebral cortex, hippocampus, basal ganglia and limbic regions; a single serotoninergic neuron may send divergent axon collaterals to a number of remote forebrain areas. Serotonin is synthesized from its precursor, tryptophan, within these serotonergic neurons where it is stored in vesicles until its release.

Release of serotonin is influenced principally by the rate of firing of the dorsal raphe nuclei (DRN), which occurs in a rhythmic, 'pacemaker'-like fashion. This is regulated by a complex system comprising inputs from other neurotransmitter systems (principally stimulatory noradrenergic inputs from the locus coeruleus, and inhibitory influences from serotonergic somatodendritic $5HT_{1A}$ autoreceptors). However, the amount of serotonin released from the axon terminals in response to action potentials at a given frequency is not constant, being heavily modified by the action of presynaptic autoreceptors and $5HT_{1B}$ terminal autoreceptors (Adrien, 1995; Gothert, 1997). Once release, free serotonin is cleared from the extracellular space by reuptake into the serotonergic neuron by a high-affinity transporter, or catabolised into 5-hydroxy-indolacetic acid (5-HIAA) by monoamine oxidase A (MAOA).

A number of endogenous or exogenous factors can also influence serotonin release in the CNS, and need to be considered when examining the serotonergic system. In animal studies, serum tryptophan concentrations have been demonstrated to have a significantly influence serotonin release, with tryptophan infusions increasing CNS serotonin and tryptphan depletion having the opposite effect (Fernstrom and Wurtman, 1971; Westerink and De Vries, 1991; Stancampiano et al., 1997). An intrinsic circadian effect on serotonin release has also been demonstrated independent of the sleep-wake cycle (Barassin et al., 2002; Malek et al., 2004). Abundant evidence from animal and human studies implicates serotonin in the regulation of mood and affect (Blier and de Montigny, 1999; Middlemiss et al., 2002), and antipsychotic and antidepressant appear to exert their effect at least in part through the serotonergic system (Stockmeier, 1997; Middlemiss et al., 2002). As might be anticipated from the involvement of serotonin in the sleep-wake cycle, stimulants drugs also appear to work through stimulation of serotonin (as well as dopamine) release. Best characterized in this

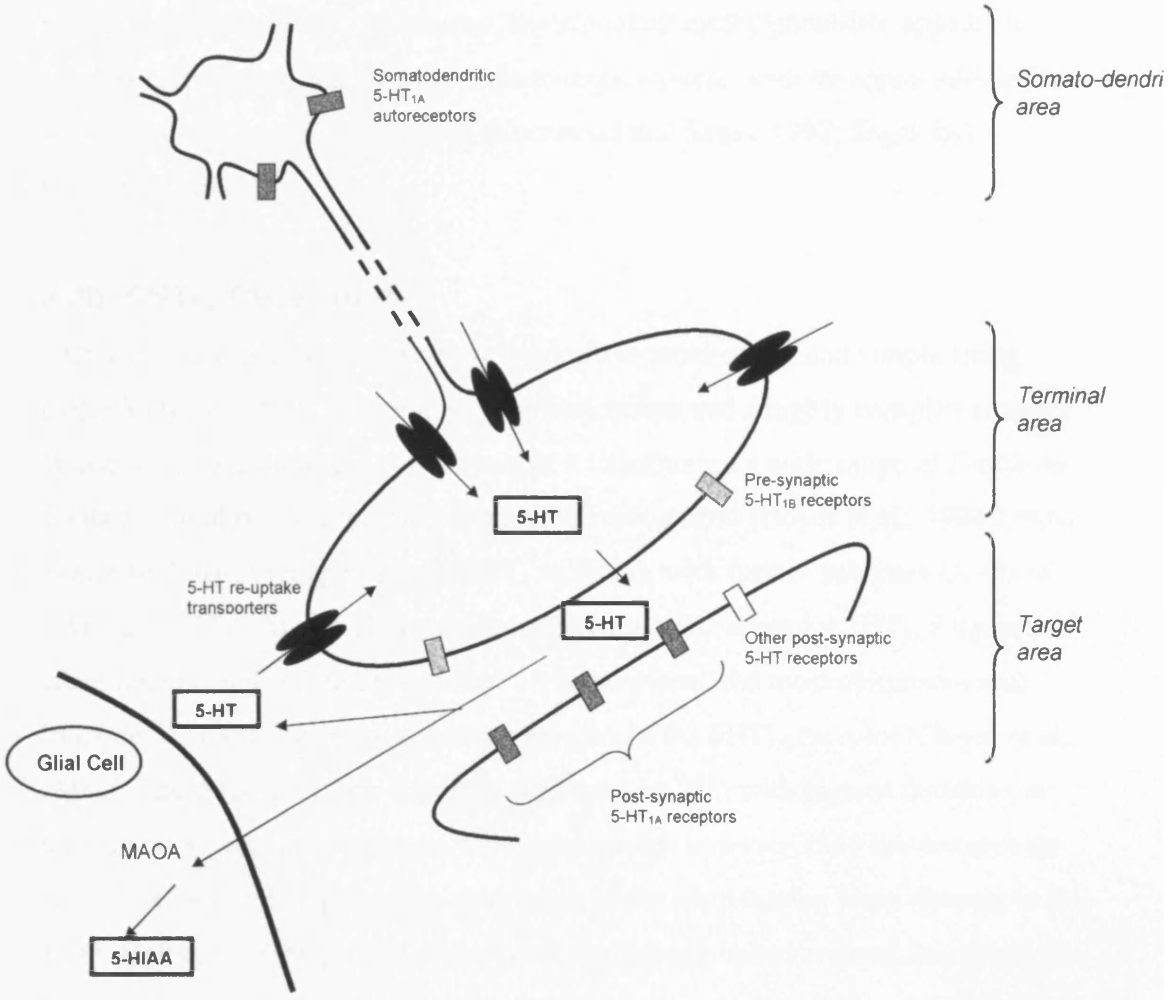


Figure 3. 7. *Schematic representation of a serotonergic neuron located in the dorsal raphe nuclei. Serotonin (5-HT) is released into the extracellular space, where it may bind to a variety of receptors, the most widespread of which are the post-synaptic 5-HT$_{1A}$ receptors. Presynaptic 5-HT$_{1B}$ receptors and somatodendritic 5-HT$_{1A}$ autoreceptors both negatively influence rates of neuronal firing. Serotonin in cleared from the extracellular space, either by reuptake into the neuron via high-affinity serotonin transporters, or through catabolism into 5-hydoxy-indolacetic acid (5-HIAA) under the control of the enzyme MAOA in glial cells.*

respect are methamphetamine and its derivatives; in animal microdialysis experiments, these drugs have been clearly demonstrated to result in substantial increases in serotonin and dopamine (Kuczenski and Segal, 1997; Segal and Kuczenski, 1997, 1999). In contrast, the stimulant methylphenidate appears to exert its effect solely through the dopaminergic system, with no appreciable effect on serotonergic neurotransmission (Kuczenski and Segal, 1997; Segal and Kuczenski, 1999).

3.3b. $5HT_{1A}$ Receptors.

Although serotonergic neurons have a primitive architecture and simple firing patterns (Jacobs, 1997), the widespread projections and a highly complex receptor system of the serotonergic system enable it to influence a wide range of functions. To date, a total of 16 serotonin receptors are recognized (Hoyer et al., 1994); these comprise 7 major receptor types ($5HT_1$ to $5HT_7$), with further subtypes (A-D) of $5HT_1$ and $5HT_2$. All are G protein coupled receptors except for $5HT_3$, a ligand-gated ion channel. Within the central nervous system, the most ubiquitous and functionally most important serotonin receptor is the $5HT_{1A}$ receptor (Hoyer et al., 1994). These receptors are found throughout the CNS, with highest densities in the hippocampus, limbic system, and raphe nuclei; however, they are *not* seen in the cerebellum, substantia nigra or striatum of the adult human brain (Burnet et al., 1995; Hall et al., 1997). $5HT_{1A}$ receptors are thought to be involved in a range of functions, but appear to have a particular role in the regulation of mood (Deakin, 1991) and sleep (Gardner et al., 1997; Seifritz et al., 1997). They are inhibitory and have a dual pattern of distribution, being located both on serotonergic neurones (somatodendritic autoreceptors) and on the targets of serotonergic projections (post synaptic receptors or heteroreceptors). There is evidence to suggest that these two forms of $5HT_{1A}$ receptor have somewhat different pharmacological profile (Millan et al., 1994); $5HT_{1A}$ somatodendritic autoreceptors are desensitized by prolonged exposure to endogenous serotonin (Chaput et al., 1986; Le Poul et al., 1995), probably resulting from receptor internalisation (Riad et al., 2001), wheras $5HT_{1A}$ heteroreceptors are not subject to such desensitisation. This difference in properties is believed to underpin the efficacy of antidepressant drugs (Blier and de Montigny, 1994).

Section 3.4: $5HT_{1A}$ receptor radioligands

A number of $5HT_{1A}$ receptor radioligands have been developed and investigated for PET imaging over the last two decades, although few have been successful enough in preclinical testing to reach the stage of human studies. Broadly speaking, these radioligands have been derivatives of either 8-OH-DPAT, a selective $5HT_{1A}$ agonist, or WAY-100635, a selective $5HT_{1A}$ antagonist.

3.4a. 8-OH-DPAT

8-OH-DPAT was the first $5HT_{1A}$ ligand developed for imaging, being radioiodinated in 1988 for use in auroradiographic studies (Gozlan et al., 1988). However, it has not been developed for use *in vivo;* agonists such as 8-OH-DPAT bind only to those $5HT_{1A}$ receptors which are G-protein-coupled, unlike antagonists which bind to both G-protein-coupled and uncoupled forms of the receptor. They therefore need a higher affinity than antagonists to reach an equivalent binding potential (B_{max}/K_d). As a result, the relatively low affinity of 8-OH-DPAT (K_d = 1.6n*M)* is probably insufficient to generate images *in vivo,* and has not been further investigated for this purpose (Passchier and van Waarde, 2001). A number of derivatives of this compound have subsequently been developed with higher affinities but have not been adopted in human studies for a variety of technical reasons (Passchier and van Waarde, 2001).

3.4b. WAY-100635

The first potent radioligand for the delineation of the $5HT_{1A}$ receptor *in vivo* was [^{11}C] WAY-100635, an antagonist which binds potently and selectively to the $5HT_{1A}$ receptor (Forster et al., 1995; Khawaja, 1995). [^{11}C] WAY-100635 has a high affinity for the receptor (inhibition constant [K_i]= 0.8nM (Zhuang et al., 1994)); along with its derivative, DWAY, WAY-100635 has been used extensively in studies of $5HT_{1A}$ receptor distribution and density (Pike et al., 1996; Ito et al., 1999; Sargent et al., 2000; Parsey et al., 2006), and due to a high affinity produces images with a high signal-to-noise ratio and good contrast. However, there are several major drawbacks with this ligand in terms of its value in clinical and research studies. Firstly, ligands labeled with the radioisotope [^{11}C]

cannot be distributed from the cyclotron to remote hospitals due to its short half life (20 minutes); secondly, the radiosynthesis process for [^{11}C] WAY-100635 is taxing (Houle et al., 2000); and thirdly, its binding appears to be insensitive to endogenous serotonin release (Maeda et al., 2001), so it has little or no value for imaging serotonin flux *in vivo*.

3.4c. MPPF

A derivative of WAY-100635, 4-2′-(methoxy-phenyl)-1-[2′-(*N*-2″-pyridinyl)-*p*-fluorobenzamido]ethlpiperazine (abbreviated to MPPF) has been developed (Zhuang et al., 1994) which appears to overcome these drawbacks. MPPF is more simple to synthesise than [^{11}C] WAY-100635 (Passchier and van Waarde, 2001), and is labeled with the positron emitter ^{18}F (Shiue et al., 1997; Le Bars et al., 1998) which has a longer half life (109.8 minutes) than [^{11}C]. Moreover, MPPF has a lower affinity for $5HT_{1A}$ receptors (K_i = 3.3nM), close to that of endogenous serotonin (K_i=4.7nM) (Zhuang et al., 1994); although this results in lower image contrast, it raises the possibility that MPPF may be sensitive to competition from endogenous serotonin.

Studies in animals confirm that [^{18}F] MPPF binds specifically and reversibly to $5HT_{1A}$ receptors (Shiue et al., 1997; Ginovart et al., 2000). Likewise, [^{18}F] MPPF studies in healthy humans show uptake in close agreement with the known distribution of $5HT_{1A}$ receptors in the human brain (Passchier et al., 2000, 2000), demonstrating the viability of this radioligand for $5HT_{1A}$ receptor imaging. Moreover, the validity of the Logan analyses and the simplified reference tissue model (using the cerebellum as the reference tissue) for quantification [^{18}F] MPPF binding to $5HT_{1A}$ receptors in the human brain have been confirmed (Passchier et al., 2001; Costes et al., 2002). As a result, neither metabolite correction nor arterial sampling are required for the evaluation of BP using [^{18}F] MPPF.

Considerable evidence from animal studies has accumulated to suggest that [^{18}F] MPPF binding to $5HT_{1A}$ receptors *in vivo* is indeed sensitive to endogenous serotonin release. Most of this work has been performed using a β^+-range-sensitive detector (Zimmer et al., 2002) in anaesthetized rats, combined with

microdialysis. Initially, Zimmer et al. showed that endogenous serotonin release, mediated by fenfluramine administration, reduces [^{18}F] MPPF binding in a dose-dependent manner (Zimmer et al., 2002). More recently they demonstrated that serotonin release evoked in a quasi-physiological manner, through electrical stimulation of the dorsal raphe nuclei, also results in reduced [^{18}F] MPPF binding (Rbah et al., 2003). Furthermore, the same group subsequently showed that decreasing endogenous serotonin release by the administration of a tryptophan hydroxylase inibitor results in an increase in [^{18}F] MPPF binding (Zimmer et al., 2003). As discussed earlier, the mechanism for this sensitivity is unclear; although the classical model of direct competition for available receptor binding sites may be relevant, it is likely to be an oversimplification of the situation. Recent animal data has suggested that internalization of receptors bound to endogenous or exogenous agonist will reduce [^{18}F] MPPF binding to $5HT_{1A}$ autoreceptors in the raphe nuclei , although this effect is not seen on heteroreceptors in the hippocampus (Riad et al., 2004; Zimmer et al., 2004).

Interestingly, there remains some debate as to whether altered [^{18}F] MPPF binding is truly detectable at physiological ranges of serotonin flux. Two studies, one in animals (de Haes et al., 2006) and one in humans (De Haes et al., 2002), have failed to demonstrate such changes. The latter study is, to date, the only human PET study which has attempted to demonstrate changes in [^{18}F] MPPF binding in the face of endogenous serotonin flux. This study has been criticisised, however, for using tryptophan infusions and tryptophan depletion in an attempt to manipulate CNS serotonin release; the timing and magnitude of CNS serotonergic changes is unpredictable with this methodology, making it impossible to draw firm conclusions regarding the value of [^{18}F] MPPF PET. In the former (animal) study, however, supraphysiological increases in serotonin were induced using fenfluramine in conscious monkeys. These changes, measured using microdialysis, were not accompanied by changes in [^{18}F] MPPF binding (de Haes et al., 2006). The authors of these two studies have suggested that the inconsistent results arise through a peculiarity of the $5HT_{1A}$ receptor, which is able to exist in a 'high affinity' and 'low affinity' state (Nenonene et al., 1994; Watson et al., 2000). Antagonists (including [^{18}F] MPPF) will bind equally to receptors in the low and high affinity states, whereas agonists (including endogenous serotonin)

will preferentially bind to receptors in the high affinity state (Nenonene et al., 1994; Watson et al., 2000). [^{18}F] MPPF binding will only alter in the presence of endogenous serotonin, therefore, if sufficient receptors are in the high affinity state. At present this remains a matter for conjecture, as this concept has not been tested. Moreover, while several studies have confirmed the value of [^{18}F] MPPF PET in measuring $5HT_{1A}$ receptor density in humans (Passchier et al., 2000; Passchier et al., 2001; Merlet et al., 2004; Costes et al., 2005), more work is required to assess its potential to measure changes in serotonergic neurotransmission in vivo.

Conclusion

PET technology has a unique capacity to measure physiological processes in the living human brain in a noninvasive fashion. While studies to date have examined regional blood flow and metabolism in sleep, the development of new ligands and modeling techniques raises the possibility of imaging neurochemical changes during the sleep wake cycle. [^{18}F] MPPF, a tracer specific to the $5HT_{1A}$ receptor, is one such ligand; while its usefulness in this setting is not yet fully proven, it may have the capacity to shed new light on changes in the human serotonergic system during sleep.

CHAPTER 4

EPILEPSY – DEFINITIONS, CLASSIFICATION AND EPIDEMIOLOGY

Introduction

Before discussing frontal lobe epilepsy, a major focus of this thesis, it is necessary to review some important general concepts in epilepsy. This chapter comprises a review of the terminology, classification and epidemiology of epilepsy, including a discussion of the current limitations in these areas. Firstly, however, some key terms should be defined.

A *seizure* is the clinical manifestation of a paroxysmal disturbance of central nervous system function, associated with excessive neuronal discharge, that is synchronous and self-limited. As such, a seizure is an individual episode, and is distinct from *epilepsy* which is defined as a tendency to recurrent, unprovoked seizures. The current ILAE definition of epilepsy is the occurrence of at least two unprovoked seizures separated in time by at least twenty four hours. An *epilepsy syndrome,* on the other hand, is defined as 'a cluster of signs and symptoms that customarily occur together' (ILAE, 1985), and is usually made on the basis of clinical, neurophysiological and neuroimaging data.

Section 4.1. Classification Systems

Epilepsy is a heterogeneous disorder; seizure type, associated comorbidities, appropriate treatment and prognosis all vary widely between affected individuals. Accordingly there is a clear need, from both clinical and research perspectives, to subclassify this condition in a manner that will assist in patient evaluation, management and prognostication. Unfortunately, however, classification of seizures and epilepsy has proved both problematic and controversial, and remains a hotly debated topic.

4.1a. Historical perspective

An attempt to classify epilepsy into subgroups was first attempted by Galen in the second century AD (Gastaut and Zifkin, 1985). Classification, however, really began in 19th Century France, where physicians at institutions such as the Salpêtrière Hospital in Paris coined terms such as 'grand mal', 'petit mal' and 'status epilepticus' ('etat de mal') (Temkin, 1994). These terms soon entered common usage and were used for many years, but no distinction was made between seizure types and epilepsy syndromes, and physicians used the terms in different ways. For example, the term 'petit mal' was meant, strictly speaking, to describe what in modern terminology are termed absence seizures; however, many physicians would use the term to describe any 'small seizure' including complex partial seizures.

4.1b. ILAE Classification systems

The first International Classification of the Epilepsies (ICE) was proposed by the ILAE in 1969 in an attempt to improve diagnostic consistency (Gastaut, 1969). This classification established a fundamental dichotomy in which epilepsies were either partial or generalised, a distinction that was made on the basis of clinical and electrographic features. Partial epilepsies were all considered to be symptomatic, wheras generalised epilepsies could be primary, secondary or undetermined. This system, while useful, was rather broad and contained a number of ambiguities.

In an attempt to improve upon this, the ILAE proposed a new classification system, the International Classification of the Epilepsies and Epileptic Syndromes (ICEES) (ILAE, 1981, 1985), which forms the basis of the current system. This required two levels of classification – one for seizures, and the other for epilepsy syndrome. The aim was a more comprehensive and pluralistic approach to classification, with the key dichotomy between partial (or 'localisation-related') and generalised epilepsies remaining, and a further subdivision into idiopathic or symptomatic categories. Once categorised in this fashion, there was a final level of classification into discrete epileptic syndromes. The term 'syndrome' was preferred to 'disease', as it does not necessarily imply a common aetiology and

prognosis within all subjects. Again, the syndrome diagnosis was made on the basis of clinical features (including seizure semiology, age at onset, and associated neuropsychological and neurological signs) in conjunction with findings from EEG and neuroimaging studies. Two additional categories were also included in this classification: epilepsies and syndromes undetermined whether focal or generalised; and special syndromes (which included febrile convulsions and isolated seizures).

The ICEES was revised in 1989 (ILAE, 1989), with some additions and clarifications, but with essentially the same structure. The main change made in this revision was to define 'idiopathic' more rigidly as referring to epilepsies with specific electroclinical characteristics and a probable genetic aetiology, and to introduce the term 'cryptogenic' for epilepsies which were likely to be symptomatic but in which no definite cause had been identified. This classification system remains in use today, and is displayed on Tables 4.1 and 4.2.

4.1c. Problems with the current classification system structure

The current classification system has been a considerable advance in the field of epileptology. It has provided clinicians and scientists alike with a common nomenclature, allowing clear and meaningful communication between both those involved in direct patient care and those involved in epilepsy research. However, there is a growing acceptance that the system is now outdated and change is required. There are several reasons for this viewpoint.

Descriptive nature. The current classification system is largely descriptive, with syndromes defined by particular electroclinical patterns but without necessarily having an underlying common pathology or prognosis. This was an intentional approach; at the time it was developed, not enough was known about aetiological and pathological processes in epilepsy to use these as the basis of a classification system. Since 1989, however, there have been considerable advances in scientific knowledge. For example, major advances in neuroimaging have revolutionised the understanding of epilepsy and provided the ability to diagnose abnormalities such as hippocampal sclerosis and malformations of cortical development *in vivo*.

1 Partial (focal, local) seizures

- 1.1 Simple partial seizures (consciousness not impaired)
  - 1.1.1 With motor signs
  - 1.1.2 With somatosensory or special sensory symptoms
  - 1.1.3 With autonomic symptoms or signs
  - 1.1.4 With psychic symptoms
- 1.2 Complex partial seizures
  - 1.2.1 Simple partial onset followed by impairment of consciousness
  - 1.2.2 With impairment of consciousness at onset
- 1.3 Partial seizures evolving to secondarily generalised seizures (tonic-clonic, tonic or clonic)
  - 1.3.1 Simple partial seizures evolving to generalised seizures
  - 1.3.2 Complex partial seizures evolving to generalised seizures
  - 1.3.3 Simple partial seizures evolving to complex partial seizures evolving to generalised seizures

2 Generalised seizures

- 2.1 Absence seizures
  - 2.1.1 Typical absence seizures
  - 2.1.2 Atypical absence seizures
- 2.2 Myoclonic seizures
- 2.3 Clonic seizures
- 2.4 Tonic seizures
- 2.5 Tonic-clonic seizures
- 2.6 Atonic (astatic) seizures

3 Unclassified epileptic seizures

Table 4. 1. *Summary of the current ILAE classification of epileptic seizures (ILAE, 1981)*

1.Localisation-related (focal) epilepsies	2. Generalised epilepsies	3. Undetermined epilepsies	4. Special Syndromes
1.1 Idiopathic • Benign childhood epilepsy with centrotemporal spikes • Childhood epilepsy with occipital paroxysms • Primary reading epilepsy 1.2 Symptomatic • Chronic progressive epilepsy partialis continua of childhood • Syndromes characterised by seiures with specific modes of precipitation • Temporal lobe epilepsies • Frontal lobe epilepsies • Parietal lobe epilepsies • Occipital lobe epilepsies 1.3 Cryptogenic	2.1 Idiopathic • Benign neonatal familial convulsions • Benign neonatal convulsions • Benign myoclonic epilepsy in infancy • Childhood absence epilepsy • Juvenile absence epilepsy • Epilepsies with generalised tonic-clonic seizures on awakening • Other idiopathic generalised epilepsies 2.2 Cryptogenic or symptomatic • West syndrome • Lennox-Gastaut syndrome • Epilepsy with myoclonic astatic epilepsy • Epilepsy with myoclonic absences	3.1 With both generalised and focal seizures • Neonatal seizures • Severe myoclonic epilepsy in infancy • Epilepsy with continuous spike-waves during slow-wave sleep • Acquired epileptic aphasia • Other undetermined epilepsies 3.2 Without unequivocal focal or generalised features	4.1 Situation related seizures • Febrile convulsions • Isolated seizures or isolated status epilepticus • Seizures occurring only with acute metabolic or toxic event • Reflex epilepsies

Table 4. 2. *Summary of the current ILAE classification of epilepsies and epileptic syndromes (ILAE, 1989).*

Such abnormalities often have important implications in terms of pathophysiology and prognosis, but are not incorporated into the framework of the current classification.

Similar problems arise with respect to the genetics of epilepsy. While the term 'idiopathic' is used in the classification system to imply a genetic basis to an epilepsy syndrome, the utility of the system in distinguishing genetic conditions is limited. For example, in the condition of Generalised Epilepsy with Febrile Seizures Plus (GEFS+), different family members with the same inherited mutation of the sodium channel α subunit gene (*SCN1A*) receptor may develop different seizure types (Scheffer and Berkovic, 1997; Wallace et al., 2001). Under the current classification, each will be diagnosed with a different syndrome, despite carrying the same fundamental biological abnormality, the genetic mutation. Conversely, in other conditions such as Autosomal Dominant Nocturnal Frontal Lobe Epilepsy (ADNFLE), indistinguishable phenotypes can arise from mutations in different genes (McLellan et al., 2003). In view of such advances in neuroimaging, genetics and other areas, a new classification system which incorporates diagnostic entities with common pathophysiologic and anatomic features, as opposed to the current syndromic approach, would be desirable.

Practical application. A further problem with the current classification structure is that some individuals with epilepsy are difficult to classify within it. They may have overlapping features of more than one syndrome (Reutens and Berkovic, 1995) or clinical features that do not clearly fit any category or syndrome. In some situations the question may be raised as to whether these cases represent new syndromes. As no clear definition exists as to what constitutes a syndrome, this somewhat arbitrary decision is based on a consensus of expert opinion, a process with limited scientific validity. This problem is exacerbated by the fundamental dichotomy between focal and generalised epilepsy syndromes in the current system. It has become increasingly apparent that there may be overlap in this area; focal seizures may be seen in some generalised epilepsies (Taylor et al., 2004) and generalised spike-wave discharges may be seen in some focal epilepsies (Beydoun et al., 1992). Although the concept of focal and generalised seizures

and epilepsies is a useful one, it is important to recognise that it is not applicable in all situations and attempting to do so may be misleading and counterproductive.

Mixing of semiological and electrographic data. The structure of International Classification of Epileptic Seizures has been criticised on the grounds that seizures are classified on the basis of ictal and interictal EEG findings in addition to clinical semiology. Luders and colleagues have stressed the fact that often clinical semiology and EEG findings are not strictly concordant, and that seizure classification should therefore be undertaken on a purely semiological basis. They make the point that the ictal semiology is analogous to a neurological sign in other disorders (e.g. tremor in Parkinson Disease), and that this information should be analysed separately to other data such as neuroimaging, clinical history and EEG findings. All information should then be integrated to define the epileptic syndrome precisely (Luders et al., 1998, 1999).

4.1d. What is the purpose of the classification system?

A more fundamental question in the debate over the classification of epilepsy is whether a classification system based on syndromic diagnoses is really the most useful approach. A key question here is what is meant by classification, and what purpose it is designed to fulfil. This was originally characterised in the writings of Hughlings Jackson (Jackson, 1932) in which he compared the classification of a botanist, based on scientific and taxonomic principles, with that of a gardener, which has a practical, utilitarian basis. Addressing the scientific aspect, Berg has compared classification in epilepsy with the biological classification of life. She has made the point that in biology classification is a highly developed discipline with clear underlying principles and rules (Wolf, 2003). This is in marked contrast to the classification of epilepsy in which there are no rules, guidelines or standards to establish what constitutes a syndrome, and until such criteria exist, the concept of an 'epilepsy syndrome' will remain a nebulous one from the scientific perspective.

Criticisms of the classification system have also been made from the practical, 'gardeners', point of view. Soon after its publication, several studies assessed the

utility of the system in clinical practice, judging this by the percentage of patients in a sample who could be classified. The majority of these studies reported very high proportions of adequately classified patients (>95%) (Loiseau et al., 1991), leading to the conclusion that the system was clinically practical and useful. However, the majority of diagnoses in such series tend to be in the broad, non-specific categories such as 'cryptogenic localisation related' and 'undetermined', rather than in the more specific syndromes. In the UK National General Practice Study of Epilepsy (Manford et al., 1992), approximately two thirds of all patients fell into these broad, non-specific categories. Moreover, one study from the Cleveland clinic (Kellinghaus et al., 2004) reported that even in this tertiary setting only 4% of adults and 21% of children had specific syndromic diagnoses, with the remainder in unspecified categories. It has, therefore, been argued by more than one author (Manford et al., 1992; Everitt and Sander, 1999),that the reported accuracy of the classification scheme is artificial. Most patients, particularly outside of specialised centres, will be categorised in one of the non-specific groups which provide very little information pertaining to aetiology, treatment or prognosis. The classification is therefore of limited value in the majority of individuals with epilepsy.

4.1e. Development of a new classification system

While most epileptologists agree that the present classification system is imperfect, there is no such agreement on how to replace it. Broadly speaking, there are two fundamental problems to overcome.

The first issue remains, as in Hughlings Jackson's time, developing a system that is scientifically meaningful but also practical enough to be used in routine neurological practice. A truly useful classification system will need to be applicable in a huge variety of research situations in addition to its function in clinical practice. It must be practical enough to be used by clinicians in the everyday diagnosis and management of patients with epilepsy, from the most straightforward cases to those patients with intractable epilepsy requiring epilepsy surgery. For research it should be precise enough to be relevant in scientific

studies of the genetic basis and pathophysiology of various forms of epilepsy, and yet simple enough to be applicable in large scale epidemiological population studies (in which many patients will not have had specialist neurological, let alone tertiary epileptological, input). The new classification system should, therefore, be capable of incorporating the enormous recent advances in the scientific understanding of epilepsy, but not be reliant on these to have clinical utility.

The second major problem arises from the need to approach epilepsy classification in a manner that is acceptable to the international epileptology community (Engel, 2001). A classification system will clearly have an impact upon the way epilepsy is conceptualised by researchers and clinicians. Unsurprisingly, many experts have differing opinions on such a conceptualisation, often influenced by their personal experience, knowledge base and research. Finding a solution that is acceptable to all, or at least the majority, of this community is a significant challenge in the development of a new classification.

As a result of these problems, work on the classification of epileptic seizures and epilepsy is still ongoing. In 2001, the ILAE Task Force on Classification and Terminology published a proposed diagnostic scheme for people with seizures and epilepsy (Engel, 2001). This was an attempt to revise the 1989 classification with purely descriptive ictal phenomenology, and while not a classification in itself, was proposed as a framework for the new classification scheme. The basis of this framework is a five-axis approach with Axis 1 being a description of ictal semiology, using a standardised glossary of terms. Axis 2 is the epileptic seizure type, representing diagnostic entities with aetiologic, therapeutic and prognostic implications. Axis 3 is the epilepsy syndrome, to be applied when possible. Axis 4 then specifies aetiology when known, and Axis 5 is a designation of the degree of impairment arising from the epilepsy. While this framework has been accepted in principle by the ILAE membership, there remains lively debate as to its usefulness (Wolf, 2003).

Section 4.2. Epidemiology of Epilepsy

Epidemiology is the study of the frequency, distribution and behaviour of a disease in populations. Numerous epidemiological studies of epilepsy have been conducted which have provided considerable information regarding its occurrence and natural history. The interpretation of much of the available data has, however, been limited by problems largely related to study methodology, and further well-conducted studies are still required.

4.2a. Incidence and prevalence

The ***incidence*** of a condition is defined as its rate of occurrence in a population, and is usually expressed in terms of cases per 100 000 of the population per year. The overall incidence of epilepsy in developed countries is in the region of 50 per 100 000 per year (Kotsopoulos et al., 2002). Within these countries, however, there are significant socioeconomic influences, with an increased incidence observed in lower socioeconomic groups (Heaney et al., 2002). In addition, studies over the last three decades indicate that the incidence of epilepsy is decreasing in children but increasing in the elderly (Everitt and Sander, 1998). It has been suggested that improved prenatal and antenatal care are responsible for the reductions in childhood , wheras the increase in the elderly is attributable to greater survival rates in individuals with stroke and cerebrovascular disease. Fewer incidence studies exist from developing countries, but available data suggests that in such areas the incidence of epilepsy is at least double that observed in developed countries (Lavados et al., 1992; Placencia et al., 1992); this finding may be related, at least in part, to endemic infections such as malaria and cysticercosis in some of these regions (Preux and Druet-Cabanac, 2005).

Prevalence is defined as the proportion of a defined population affected with a condition at a point in time, and is usually expressed as the number of cases per 1000 population. Studies from around the world indicate prevalence rates of 4-10 per 1000 (Sander, 2003), with studies in developing countries reporting prevalence at the higher end of the spectrum; the highest rates appear to be in the rural regions of developing countries. When lifetime prevalence (as opposed to prevalence of

active epilepsy) is considered, rates are much higher. Up to 5% of the population will experience at least one non-febrile seizure in their lifetime, a consistent finding in both developed and developing nations (Sander and Shorvon, 1996).

4.2b. Prognosis

Prognostic studies have addressed both the potential for remission and the mortality in epilepsy. An estimated 70% of individuals with epilepsy will enter remission at some point in their condition (Sander and Shorvon, 1996), with the dominant predictor of remission being the number of seizures in the early months after presentation (MacDonald et al., 2000). Seizure type does not seem to influence prognosis, but there is insufficient data from available studies to make any definitive statement about the importance of aetiology or epilepsy syndrome as factors. Mortality studies have shown that, despite the generally good prognosis for seizure control, individuals with epilepsy are at increased risk of death compared to those without. The overall standardised mortality ratio in epilepsy has been estimated at 2.5 – 3 (Cockerell et al., 1997; Shackleton et al., 1999; Shackleton et al., 2002), but this figure is higher in individuals with refractory symptomatic epilepsy and intellectual disability. Suicide (Nilsson et al., 2002) and Sudden Unexplained Death in Epilepsy (SUDEP) (Pedley and Hauser, 2002) as well as trauma, status epilepticus and pneumonia (Sander, 2003) have all been identified as significant causes of death in epilepsy.

4.2c. Methodological problems

It is crucial that sound study methodology is employed if epidemiological studies are to provide valid and meaningful information. Unfortunately, however, in many studies of the epidemiology of epilepsy this has not been the case. Suboptimal methodologies have resulted in a number of inconsistencies between some studies, and some questionable findings (Kotsopoulos et al., 2002). The methodological issues fall into a number of areas.

A fundamental problem has resulted from the fact that different investigators, particularly in older studies, have used different definitions of epilepsy and

different classification models. This clearly makes comparison of the findings in different studies difficult or impossible. To address this issue, in 1997 the ILAE published guidelines for epidemiologic studies (Toczek et al., 1997) and these have been supplemented by recommendations arising through major meta-analyses (Kotsopoulos et al., 2002). The guidelines consist of a list of definitions for seizures, seizure types, aetiological factors and indices of measurement that should be adopted for use in such studies.

A second issue is that of study design. Ideally studies should be prospective in design, with attention paid to methods of case ascertainment, as such methods will impact strongly on the accuracy of the results. For example, if data is collected exclusively from specialist neurological centres it is likely to be accurate and complete from a diagnostic point of view; this sample, however, will be biased by referral patterns and will therefore be unlikely to reflect the patterns of epilepsy in the population as a whole. On the other hand, community-based studies, such as the UK General Practice Study of Epilepsy (Cockerell et al., 1997) and the Rochester Epidemiology Project (Zarrelli et al., 1999) will give a more accurate reflection of epilepsy in the population, but diagnostic accuracy in such studies may be lower. Also, even in these studies, there may be individuals who have seizures but are either unaware of them or simply do not report them, resulting in inaccuracies in the findings.

A further, and related, problem is that of diagnostic accuracy. A definitive diagnosis of epilepsy is not always straightforward to make, being based almost entirely on the clinical history. As such it is strongly reliant on both the quality of the available seizure descriptions and the proficiency and experience of the clinician (Sander, 2003). This problem will be compounded in studies attempting to address specific syndromes in which additional factors, such as access to diagnostic technology and specialist services, will also be relevant. As outlined above, there may often be some trade-off in studies between diagnostic accuracy and optimal case ascertainment - obtaining both within a study may be difficult to achieve.

4.2d. Outstanding issues:

There remain epidemiological aspects of epilepsy which have not been well studied to date. A major inadequacy is the lack of good quality incidence and mortality studies in developing countries (Toczek et al., 1997); of those studies which have been performed, many are methodologically suboptimal being either cross-sectional or retrospective in design (Preux and Druet-Cabanac, 2005). Large scale prospective studies are still needed to help understand differences in epilepsy in these regions compared to the developed world.

Another major shortcoming, and one that applies to all regions of the world, is the paucity of data regarding individual epilepsy syndromes. While broad aetiological classifications have been used in some studies in developed countries (Manford et al., 1992), there exist relatively few well designed, prospective studies which have attempted to accurately and comprehensively classify patients. As a result, little is known about the incidence and prevalence of individual epilepsy syndromes in the general population. Other specific issues, such as SUDEP and the impact of drug treatment on prognosis, also require further epidemiological study (Toczek et al., 1997; Sander, 2003).

Conclusion

The epilepsies are a complex group of disorders with variable presentations, prognoses and comorbidities. The study of these conditions requires clear, commonly applicable definitions and classification systems, and a sound understanding of their epidemiology.

The 1989 ILAE classification system for seizures and epilepsy represented a major advance in epileptology. It has provided clinicians and researchers alike with a common nomenclature for use in the heterogeneous group of conditions which fall under the umbrella term "epilepsy". The challenge now, however, is to replace it with a system that incorporates the recent advances in scientific knowledge. Achieving such a system, which has both clinical utility and scientific validity, is by no means straightforward. Despite the enormous progress in scientific

knowledge that has been made since the time of Hughlings Jackson, the modern challenge in classification remains to find a system that is valid and appropriate for both "gardeners" and "botanists".

From an epidemiological perspective, while much has been learned about the occurrence and distribution epidemiological studies, considerable challenges remain. Long-term, population-based, prospective studies with attention to syndromic diagnosis are still required in developed countries, but this need is even greater in the developing world. Such studies will be major undertakings but, if well conducted, may contribute substantially to our understanding of the epilepsies.

CHAPTER 5

SLEEP AND EPILEPSY

Introduction

Sleep and epilepsy are intimately related. While sleep and sleep deprivation are undeniably important factors in the precipitation of seizures, particularly in certain epilepsy syndromes, there are also important effects in the opposite direction; epilepsy may disrupt sleep, either directly through seizures and epileptiform activity, or indirectly through medication related effects. Here I shall review the important interactions between the physiological state and the pathological condition, firstly reviewing the effects of sleep on epilepsy and subsequently the effects of epilepsy on sleep.

Section 5.1: The effects of sleep on epilepsy

The first major study of sleep and epilepsy was performed on Gowers in the late 19^{th} century. In a study of institutionalized patients, he noted that in 21% of patients, seizures occurred only at night, in 42% they occurred only during the day, and in the remaining 37% they occurred randomly either during the day or at night (Gowers, 1885). Subsequent work into the influence of sleep on epilepsy has identified a complex picture, and identified a number of relationships.

One of the earliest recognized concepts was that of the 'pure sleep epilepsy'. This term is used in those patients in whom seizures are limited exclusively to sleep; it is a relatively uncommon, being seen in about 6% of epilepsy patients admitted to a neurology department in one study (Young et al., 1985). Pure sleep epilepsies do not belong to any single epilepsy syndrome, but in general appear to respond well to treatment with antiepileptic drugs (Yaqub et al., 1997). In other cases, seizures are seen predominantly but not exclusively in sleep, and these constitute a further 4% of individuals with epilepsy; in other words, seizures occur predominantly or exclusively in sleep in around 10% of epilepsy patients (Young et al., 1985).

A separate relationship, first identified by Janz, is that of the 'awakening epilepsy' (Janz, 1962). In these cases, individuals show a tendency to have seizures occur around awakening, usually within the first hour or two after arousal. Such a pattern is commonly seen in some idiopathic generalized epilepsy syndromes.

Finally, a relatively common but non-specific relationship between epilepsy and sleep is a modification of the electroclinical manifestations of the epilepsy depending upon the sleep-wake cycle. EEG abnormalities, seizure types and seizure frequencies may all be influenced by the sleep-wake state in variety of ways.

While there are many unexplained aspects in these relationships, overall they appear to depend largely upon two factors: firstly, the epilepsy syndrome; and secondly, the stage of sleep. In addition, sleep deprivation can influence both the electrographic features of the interictal state, and the precipitation of seizures.

5.1a. Epilepsy syndrome.

There are a number of syndromes in the ILAE classification in which clear relationships of seizures to sleep have been observed, and these are listed in Table 5.1.

Idiopathic Generalised Epilepsies (IGE). Broadly speaking, the seizures of idiopathic generalized epilepsy occur during wakefulness, and are commonly 'awakening epilepsies' as described by Janz (Janz, 1962; Herman, 2002). In particular, the syndromes of Juvenile Myoclonic Epilepsy and Epilepsy with Generalised Tonic Clonic Seizures on Awakening are classical awakening epilepsies. Seizures in these syndromes also occur more commonly following nights of sleep deprivation, for reasons that are not well understood. On EEG, generalized epileptiform discharges tend to be most frequent during NREM sleep and least frequent in REM (Niedermeyer, 1965; Lieb et al., 1980; Sammaritano et al., 1991; Niedermeyer, 1996). The spike-wave discharges are most prominent in stage 2 sleep, where they are often seen in conjunction with K complexes. According to Niedermyer, these K complexes tend to have an abnormal

Idiopathic Focal Syndromes	Idiopathic Generalised Syndromes	Symptomatic Focal Syndromes	Symptomatic Generalised Syndromes	Syndromes unclear whether focal or generalised
Benign childhood epilepsy with centro-temporal spikes	Juvenile Myoclonic Epilepsy	Frontal Lobe Epilepsy	Lennox Gastaut Syndrome (tonic seizures)	Epilepsy with Continuous spike-wave during slow wave sleep
Benign childhood epilepsy with occipital paroxysms	Epilepsy with Generalised Tonic Clonic Seizures on Awakening	Nocturnal Frontal Lobe Epilepsy	West Syndrome (infantile spasms)	Landau-Kleffner syndrome
Autosomal Dominant Nocturnal Frontal Lobe Epilepsy (ADNFLE)		Temporal Lobe Epilepsy (including Nocturnal Temporal Lobe Epilepsy)		

Table 5.1 *Epilepsy syndromes with a clearly recognised relationship with sleep*

morphology with a frontal predominance, and he has proposed that this pattern represents 'dyshormia', or disordered arousal (Niedermeyer, 1996). A small subgroup of up to 10% of individuals with IGE may present as pure sleep epilepsies, with generalized tonic-clonic seizures restricted to sleep. In these individuals EEG abnormalities are often only seen during sleep (Young et al., 1985; Chokroverty, 1998).

Symptomatic Generalised Epilepsies (SGE). In contrast to IGE, the seizures of symptomatic generalised epilepsy occur in both wakefulness and sleep. However, the electroclinical manifestations may be significantly influenced by the sleep-wake state. In West syndrome, the characteristic high amplitude 'hypsarrhythmic' interictal EEG pattern is seen most prominently in early NREM sleep (Niedermeyer and Lopes da Silva, 2004). The infantile spasms of this condition also show some relationship to sleep, being seen predominantly on awakening or during drowsiness before sleep onset, although they are uncommon during sleep itself. (Kellaway et al., 1979). In contrast, the tonic seizures of Lennox Gastaut Syndrome, occur much more frequently during NREM sleep than wakefulness. They may be very subtle or clinically silent during sleep but are often very frequent, being associated with characteristic paroxysmal fast activity; such sleep-related tonic seizures are seen in over 90% of patients with (Gastaut, 1974). In addition to the influence of sleep on seizures in Lennox-Gastaut syndrome, there is facilitation and modulation of the interictal slow spike-wave pattern during sleep (Baldy-Moulinier et al., 1988).

Idiopathic Focal Epilepsies. Seizures in the idiopathic focal epilepsy syndromes of childhood have a tendency to occur during sleep. Benign childhood epilepsy with centrotemporal spikes is associated with partial or secondarily generalized seizures, which occur exclusively from sleep in 70-80% of cases (Eeg-Olofsson, 2002). On EEG, the interictal epileptiform discharges of this condition are often infrequent or absent during wakefulness, but are markedly activated during drowsiness and light NREM sleep (Niedermeyer and Lopes da Silva, 2004). In benign childhood epilepsy with occipital paroxysms (particularly of the Panayiotopoulos syndrome subtype), partial seizures, sometimes with secondary generalization, may also occur during sleep. Likewise, the interictal occipital

sharp waves are accentuated by NREM sleep (Loiseau, 2001). Autosomal Dominant Nocturnal Frontal Lobe Epilepsy (ADNFLE), while not a benign focal epilepsy of childhood, is another example of an idiopathic focal epilepsy with predominantly nocturnal seizures; this syndrome will be discussed in detail later in a later chapter of this thesis.

Symptomatic and Cryptogenic Focal Epilepsies. The so-called pure sleep epilepsies are more commonly focal than generalized. Around 80% of such cases are associated with a focal epilepsy syndrome (Yaqub et al., 1997), most commonly temporal or frontal lobe epilepsy; syndromes of nocturnal frontal lobe epilepsy, discussed in detail later (Provini et al., 1999), and nocturnal temporal lobe epilepsy (Bernasconi et al., 1998) have been well described. Frontal lobe seizures occur more commonly during sleep than temporal lobe seizures, although the latter are much more likely to secondarily generalize in sleep (Bazil and Walczak, 1997; Crespel et al., 1998; Herman et al., 2001). Interestingly, idiopathic or lesion-negative focal epilepsies appear more likely to remain strictly nocturnal than those with an associated lesion (D'Alessandro et al., 1983).

In focal epilepsies, deep (stage 3 and 4) NREM seems to be most effective in facilitating epileptiform discharges (Sammaritano et al., 1991; Malow et al., 1998). As well as being more frequent during NREM sleep, there is often extension of the field of the discharges (Sammaritano et al., 1991). In contrast, discharges in REM sleep have a more restricted field; some authors have asserted that the field in REM sleep is the most reliable interictal indicator of the epileptogenic zone (Sammaritano et al., 1991; Sammaritano, 1998).

Epilepsies undetermined as to partial or generalized. Epilepsy with continuous spike-waves during slow-wave sleep (CSWS) and Landau-Kleffner syndrome are two related syndromes which are undetermined as to whether they are partial or generalized under the current ILAE classification (ILAE, 1989). Both disorders are characterized by almost continuous subclinical spike wave activity on EEG during sleep, accompanied by neuropsychological deterioration, and represent age-related epileptic encephalopathies. In CSWS, this activity is associated with predominantly nocturnal focal motor seizures, although absences may also be seen

in wakefulness in some patients (Tassinari et al., 2000); the neuropsychological impairment may be global or selective for cognitive or expressive functions, and motor deficits such as ataxia, dystonia or hemiparesis may occur (Tassinari et al., 2000). Landau-Kleffner syndrome is characterized by a specific neuropsychological deficit, verbal auditory agnosia, which is sometimes seen in conjunction with other types of aphasia (Soprano et al., 1994). Seizures are not invariably seen, and the EEG findings are very similar to those of CSWS; the commonalities between these two disorders has led some authors to suggest that they are in fact different subclasses of a single condition (Tassinari et al., 2002; Smith and Hoeppner, 2003).

5.1b. Sleep Stage. While epilepsy syndrome is a key factor in the relationship between sleep and epilepsy, the other major aspect is sleep stage. In general, NREM sleep appears to facilitate both seizure onset and seizure spread, wheras REM sleep appears to suppress seizures. Essentially, NREM sleep is characterized by increasing cerebral hypersynchrony; in slow wave sleep, virtually every cell in the brain is discharging synchronously (Steriade et al., 1993). This state facilitates both the appearance of interictal epileptiform discharges and the onset of seizures, wheras very low rates of seizure onset (0-5%) have been reported during REM sleep (Herman et al., 2001; Minecan et al., 2002). Focal seizures (particularly those arising in the temporal lobe) secondarily generalize much more frequently during sleep compared to wakefulness (Bazil and Walczak, 1997), presumably reflecting this increased synchronization.

Interictal epileptiform discharges become increasingly frequent with increasing depth of NREM sleep, being most often seen in stage 3 and 4 slow wave sleep (Sammaritano et al., 1991; Malow et al., 1998). In contrast, while most sleep-related seizures also occur in NREM sleep, they are clearly most common in stage 2 sleep (61-68%), with lower rates (9-14%) in stages 3 and 4 (Herman et al., 2001; Minecan et al., 2002). The propensity to seizure occurrence in NREM sleep is apparently not solely a reflection of increased neuronal synchrony - if this were the case stage 3 and 4 sleep should have the highest rate of seizures. K-complexes, sleep transients seen during stage 2 sleep, have been clearly associated

with electroclinical epileptic phenomena (Halasz, 1981; Niedermeyer E., 2004). It has been demonstrated that the appearance of these phenomena is related to a pattern of periodic arousal instability within NREM sleep, termed the 'cyclic alternating pattern' or CAP (Terzano et al., 1985). Essentially CAP is identified by repetitive stereotyped EEG patterns (including vertex waves and K-complexes) lasting <60 sec and separated by time-equivalent intervals of background activity with relatively few sleep transients. As such, the CAP cycle is composed of two phases, each of up to one minute in duration: phase A, which is characterized by relative arousal and the appearance of sleep transients; and phase B, which is a period of reduced arousal. These phases, which are said to reflect arousal instability, alternate during periods of 'CAP sleep'(Terzano et al., 1991; Manni et al., 2005); they occur most prominently around periods of transition between sleep stages. CAP sleep alternates with longer periods of non-CAP sleep in which there is relative NREM stability. A number of studies have demonstrated that nocturnal seizures, particularly those occurring in clusters, occur predominantly during phase A CAP, and this feature may explain why seizures in sleep have been found to occur most commonly at times of sleep stage transition (Sammaritano, 1995). Such a relationship between CAP and seizures has also been established specifically in nocturnal frontal lobe epilepsy (NFLE), a not unexpected finding in view of the clusters of sleep-related seizures seen in this condition (Zucconi et al., 2000).

5.1c. Sleep deprivation. Sleep deprivation is well recognized as a precipitant for seizures and epileptiform discharges, a feature first reported by Gibbs and Gibbs (Gibbs and Gibbs, 1947). While the mechanisms responsible for its efficacy remain debatable, it is used clinically as a standard procedure for EEG activation.

In terms of interictal discharges, sleep deprivation may induce NREM sleep which, as discussed above, facilitates the appearance and propagation of these phenomena. However, sleep deprivation may have EEG activating effects independent of the propensity to induce drowsiness and sleep, through increasing neuronal excitability (Ellingson et al., 1984). Some authors have emphasized

differing benefits of sleep deprivation depending on the epilepsy syndrome. In idiopathic generalized epilepsy, the short fluctuations in level of awareness induced by maintaining wakefulness during the recording may be particularly useful for facilitating discharges; in focal epilepsy, on the other hand, the deeper stages of NREM sleep which may be reached if the patient is allowed to sleep following sleep deprivation may be more useful (Niedermeyer and Lopes da Silva, 2004).

While most studies in this area have examined the effect of sleep deprivation on EEG abnormalities, sleep deprivation also appears to precipitate seizures. Observational studies, many of which have looked at seizure in military personnel, consistently implicate sleep deprivation in the onset of isolated seizures, although stress and alcohol or drug consumption are also important in such cases (Bennett, 1963; Gunderson et al., 1973; Friis and Lund, 1974). Other studies have also identified sleep deprivation as a trigger for seizures in epilepsy patients (Rajna and Veres, 1993; Frucht et al., 2000), although interestingly it does not seem to influence the rate of seizure occurrence in patients admitted for video EEG monitoring (Malow et al., 2002). This finding may be a group effect, reflecting the intractable nature of the such patients, but it may imply that sleep deprivation alone (without other stressors of day to day life) is a less potent precipitant of seizures than when it is combined with other factors such as stress, drugs or alcohol.

Section 5.2: The effects of epilepsy on sleep

While sleep has a significant influence on epilepsy, a reciprocal effect is also seen, with epilepsy and antiepileptic drugs also affecting sleep in individuals with epilepsy.

5.2a. Seizures and sleep

There is considerable evidence that seizures interfere with normal sleep architecture. This phenomenon is thought to be largely responsible for the

insomnia and daytime somnolence which follows both diurnal and nocturnal seizures, and may last for well beyond the post-ictal period *per se.*

A number of studies have looked at the effects of nocturnal focal or generalized seizures on sleep architecture in both adults and children, with broadly similar results. The most consistent finding is a reduction in REM sleep of up to 50% on nights with seizures, along with increased REM latency (Baldy-Moulinier, 1982; Besset, 1982; Touchon et al., 1991). In addition, reduced sleep efficiency and total sleep time, increased sleep fragmentations with recurrent arousals, and a reduction in slow wave sleep have been observed on these nights. These disturbances are likely to be the cause of the subjective and objective sleepiness observed on the day following a nocturnal seizure (Bazil and Walczak, 1997). In frontal lobe epilepsy, disruption of sleep architecture may be a particular issue due to the large number of seizures which often occur per night (Provini et al., 1999); treatment of seizures in these patients may result in significant improvements in a number of sleep parameters including REM sleep duration, slow wave sleep duration and sleep efficiency (Tachibana et al., 1996). In addition to the effects of nocturnal seizures, diurnal seizures have also been shown to affect sleep architecture on the night following the seizure, resulting in reductions in both REM sleep and NREM sleep (Bazil et al., 2000; Vaughn and D'Cruz, 2004). These findings suggest that the functional disturbances of sleep caused by seizures may extend beyond the immediate postictal period.

It appears likely that these effects on sleep architecture result from a temporary disruption of the brainstem neurotransmitter systems modulating sleep state (see previous chapter), with REM sleep being the most susceptible state (Bazil, 2002). There is considerable evidence that discharges of generalized seizures and propagation of partial seizures involve brainstem structures (Walker, 1956; Wada, 1960), and it is possible that this involvement results in the sleep dysfunction observed.

5.2b. The interictal state and sleep

While the effect of seizures themselves on sleep is unequivocal, the effect of the interictal epileptic state is less clear. Some studies have identified changes in sleep architecture in seizure-free patients with epilepsy (Touchon et al., 1991; Sammaritano, 1996; Maganti et al., 2005). One such study found that untreated patients with IGE or focal epilepsy had reduced sleep efficiency, reduced SWS and increased stage shifts compared to controls; these abnormalities improved after treatment with antiepileptic drugs (Touchon et al., 1991). Some abnormalities in sleep architecture, such as reduced REM latency, have also been associated with daytime behavioral changes in seizure-free children (Maganti et al., 2005). It is possible that interictal discharges influence sleep architecture through increased arousals and increased stage shifts (Peled and Lavie, 1986), but other authors have found interictal discharges to be only rarely associated with arousals (Malow et al., 1998). While a number of abnormalities have been identified in the interictal state, studies in this area are often difficult to interpret. This is particularly true when sleep architecture in epilepsy is compared with that of normal controls, as these studies are frequently confounded by the presence of antiepileptic drugs (AEDs) which have effects of their own on sleep architecture (Sammaritano and Sherwin, 2000).

Section 5.3: Sleep and antiepileptic drugs

In addition to the effects of seizures and the interictal state, independent effects of antiepileptic drugs on sleep have been observed. Although the anticonvulsant effects of many of these drugs is incompletely understood, the majority appear to exert their clinical effects through influences on sodium or calcium channels, or by modulating GABA or glutamate neurotransmission (Sammaritano, 2002); these effects appear to influence sleep processes in many cases. The effects on sleep of the 'classical' antiepileptic drugs (AEDs) such as carbamezapine, valproate and phenytoin have been most widely studied, but data is also available into the effects of some newer drugs such as lamictal and gabapentin.

As with all studies in this area, a number of confounding factors are present in many AED studies in sleep – in patients with epilepsy it is often difficult to be sure what effects are due to the drug itself and which reflect improved or altered epileptic control. Studies in normal controls, on the other hand, are often small in size and only examine short-term effects of the drugs. However, through a combination of study designs, patterns of sleep alteration associated with many AEDs have become apparent. For example, carbamazepine appears to consolidate sleep, reducing awakenings and arousals, while increasing SWS and reducing REM (Yang et al., 1989; Gann et al., 1994; Gigli et al., 1997; Sammaritano and Sherwin, 2000). Phenytoin, on the other hand, may disrupt sleep causing increased arousals and reducing REM; it may also increase slow wave sleep in short-term use, although these effects become less prominent with chronic use (Roder-Wanner et al., 1987; Declerck and Wauquier, 1991). Valproate has predominantly sleep stabilizing properties, although some patients on this drug may have an increased frequency of arousals (Findji, 1982; Dadmehr et al., 1987).

The newer AEDs in general have fewer negative effects on sleep and some have positive effects. For example, gabapentin reduces awakenings during sleep and increases both REM and slow wave sleep (Rao et al., 1988; Placidi et al., 2000; Placidi et al., 2000); lamotrigine appears to stabilize sleep, increasing REM while reducing stage shifts and total SWS, without effects on daytime sleepiness (Placidi et al., 2000); and levetiracetam has been found to have little if any effects on sleep architecture (Bazil et al., 2005). The role of these effects on the side effect profile and efficacy of these drugs is, however, unclear.

Conclusion

Sleep and epilepsy are intimately related, with mutual and reciprocal interactions. While sleep or sleep deprivation may result in deteriorating seizure control, seizures, as well as the interictal state and AED therapy, may have profound effects on sleep. An appreciation of these interactions is essential when considering specific sleep-related epilepsy syndromes such as nocturnal frontal lobe epilepsy.

CHAPTER 6

FRONTAL LOBE EPILEPSY
Functional Anatomy of the Frontal Lobes

Introduction

The major focus of this thesis is the relationship between frontal lobe epilepsy (FLE), sleep and benign sleep disorders. To effectively study FLE, an appreciation of the structural and functional anatomy of the frontal lobes is required. These structures are large, accounting for 30-50% of brain mass and volume, and are involved in numerous neurological and neuropsychological processes. Many of these concern higher level cognitive functioning, and some authors have argued that it is the frontal lobes which define us as human (Stuss and Levine, 2002). This chapter addresses the gross anatomy and localisation of function within these complex structures.

Section 6.1. Gross anatomy.

The frontal lobe is the largest in the human brain. It occupies the entire area anterior to the central sulcus and superior to the lateral sulcus on the lateral surface. Medially it envelopes the anterior part of the corpus callosum and is bounded posteriorly by an imaginary line drawn between the central sulcus and the corpus callosum. The inferior surface of the frontal lobe lies on the orbital plate of the frontal bone.

The convexity of the frontal lobe is divided into four gyri: the precentral gyrus, the superior frontal gyrus, the middle frontal gyrus and the inferior frontal gyrus (Figure 6.1). The precentral gyrus lies anterior to the central sulcus on the convexity of the frontal lobe; on the medial aspect it is contiguous with the paracentral lobule. The remainder of the the lateral surface of the fontal lobe is divided into the superior, middle and inferior frontal gyri, which are oriented parallel to each other and approximately perpendicular to the precentral gyrus. The superior frontal gyrus runs above the superior frontal sulcus, and continues onto the medial aspect of the frontal lobe as far as the cingulate sulcus.

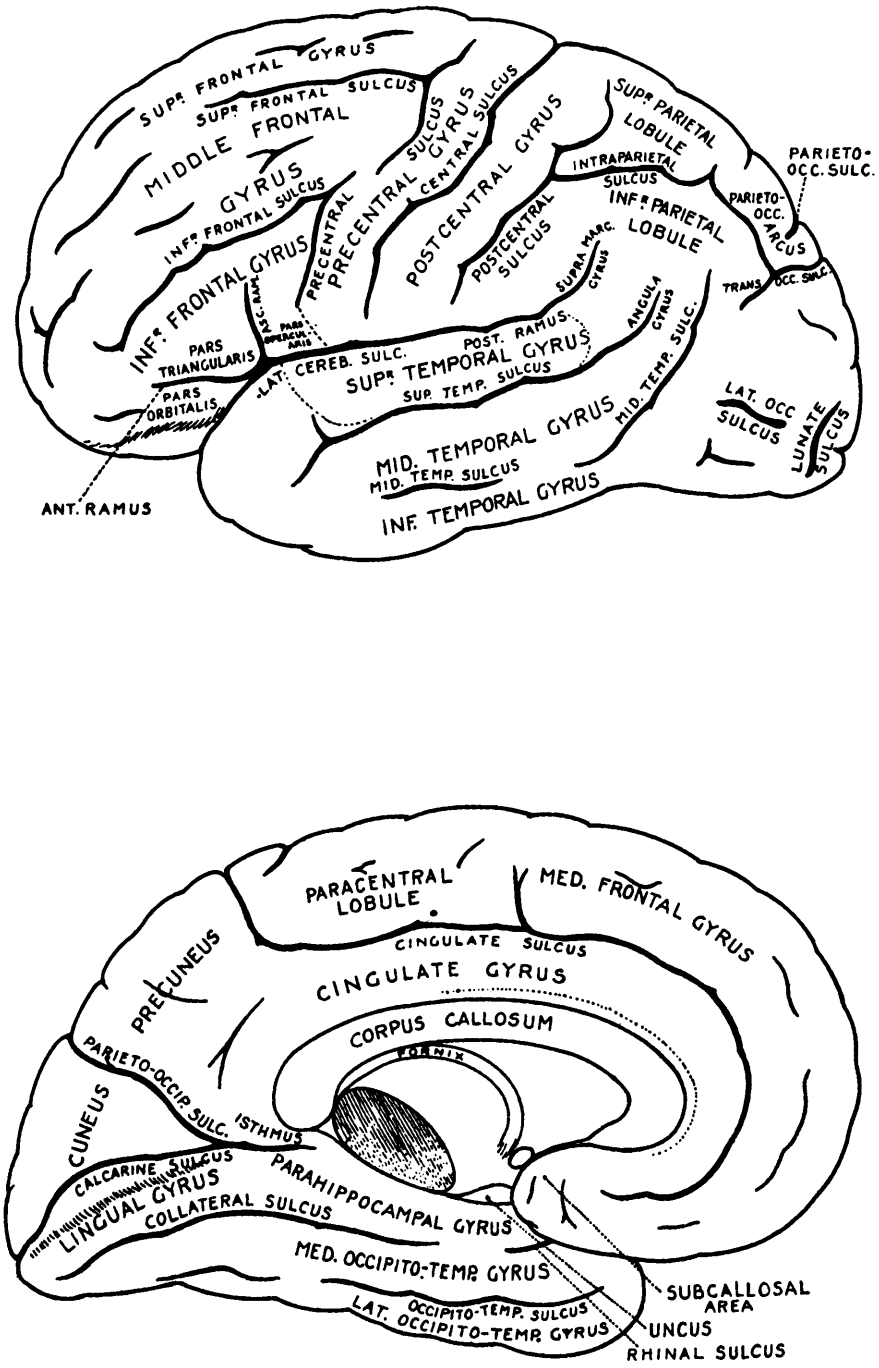


Figure 6. 1. *Medial and lateral aspects of the left cerebral hemisphere, showing the major sulci and gyri (Williams and Warwick, 1980).*

The middle frontal gyrus lies between the superior and inferior frontal sulci. The inferior frontal gyrus lies below the inferior frontal sulcus, and is visibly divided into three parts: (i) the orbital part, which is most anterior and is continuous with the orbital (inferior) surface of the frontal lobe; (ii) the opercular part, which is most posterior and constitutes part of the frontal operculum; and (iii) the triangular part, which lies between the other two.

The cingulate gyrus lies on the medial aspect of the frontal lobe, between the corpus callosum and the cingulate sulcus; the anterior part of this gyrus is structurally part of the frontal lobe; functionally it is usually considered as part of the limbic system.

The inferior aspect of the frontal lobe consists of a variable group of gyri known collectively as orbitofrontal cortex. The only consistent gyrus in this region is the gyrus rectus, which is the most medial gyrus on the orbitofrontal cortex and is separated from the other gyri by the olfactory sulcus.

Section 6.2. Functional Anatomy

Notwithstanding the gross anatomy of the frontal lobe, regional divisions within this lobe are largely defined in terms of traditional cytoarchitectonics and cortical function. While some regions (such as the primary motor cortex) have relatively tight anatomical boundaries, others (including the SMA) are relatively poorly defined anatomically. In functional terms, the various regions in the frontal lobes are largely concerned with motor activity, judgement and foresight, and mood and affect.

6.2a. Primary Motor Area

The primary motor area (M1) is located in the precentral gyrus; it corresponds to Brodmann's area 4 and is characterized by Betz cells (Figure 6.2). The main sources of input to this are the premotor cortex, primary sensory cortex, and the ventral lateral thalamic nucleus (which receives major afferent inputs from the cerebellum). The main efferent pathways from M1 are the corticospinal and

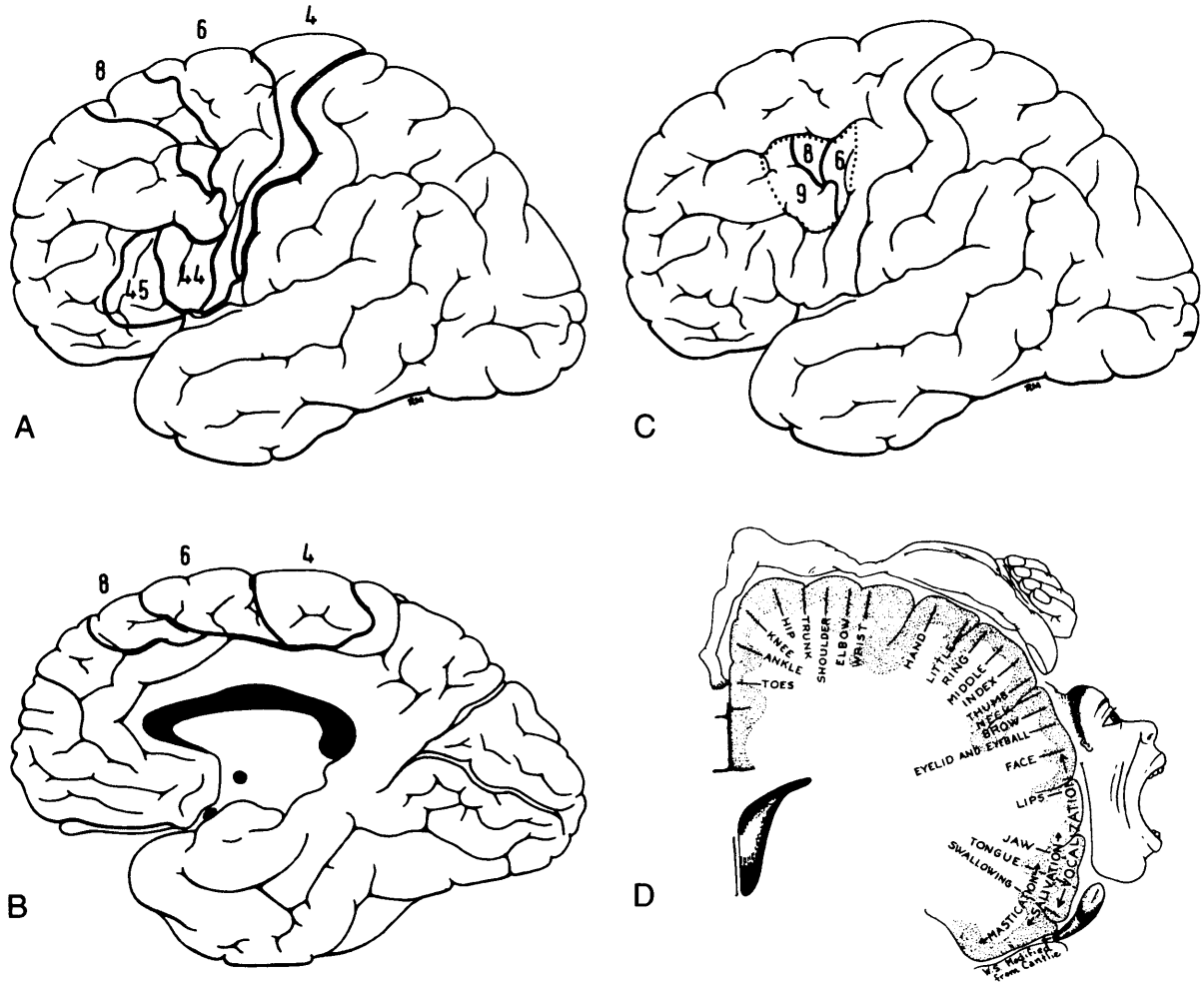


Figure 6. 2. *Important functional neuroanatomy of the frontal lobes (Williams and Warwick, 1980).* ***Panels A and B*** *show Brodmann's area 4 (corresponding to primary motor cortex), 6 and 8 (which correspond to premotor and supplementary motor cortex), and 44 and 45 (corresponding to the motor speech area of Broca.* ***Panel C*** *shows the frontal eye field (FEF), corresponding to parts of Brodmann's areas 6, 8 and 9.* ***Panel D*** *shows the motor homunculus with somatotopic representation in the primary motor cortex (Penfield and Rasmussen, 1950).*

corticobulbar tracts, which comprise the pyramidal system. About 30% of pyramidal tract fibres originate in this region. Electrical stimulation of M1 elicits contraction of muscles on the opposite side of the body. The classical stimulation studies of Penfield (Penfield, 1954) demonstrated a consistent and reproducible cortical representation of the body in the primary motor cortex; this homunculus is shown in Figure 6.2. The size of the area of cortex assigned to a particular region of the body is loosely proportional to the level of motor dexterity required for normal functioning of that region (e.g. large areas for mouth and hand, small areas for trunk and shoulder).

Destructive lesions of primary motor cortex result in paresis of voluntary movements for the corresponding area of the body. Recovery of function may occur, possibly related to functional cortical reorgansation (Ward, 2004). Residual deficits tend to be most prominent in the distal parts of the limbs and particularly affect skilled movements.

6.2b. Premotor Area

The premotor area (PMA) constitutes that part of Brodmann's area 6 located on the lateral convexity of the hemisphere, and may also invove part of area 8 (Figure 6.2). It has a different cytoarchitectonic appearance to M1, with a heterotopic agranular composition. It is widely connected with other cortical regions, but also receives inputs from the anterior division of the ventral lateral nucleus of the thalamus, which itself receives inputs from the striatum.

The PMA contributes to the pyramidal tracts directly, and also influences the primary motor cortex. It is involved in generating motor programs for actions, particularly those which are guided by sensory inputs such as visual and tactile stimuli (Roland and Zilles, 1996). While the primary motor cortex is responsible for the execution of movements, the premotor area directs the primary motor cortex in its execution. Unlike the primary motor cortex, the PMA is involved in both ipsilateral and contralateral distal movements (Roland et al., 1980).

6.2c. Supplementary Motor Area

The Supplementary Motor Area (SMA) has been widely studied, with much of the initial work being performed by Penfield and his co-workers (Penfield and Welch, 1951). It is not strictly defined anatomically, but corresponds broadly to that part of Brodmann's area 6 that lies on the medial aspect of the hemisphere, and has the same cytoarchitecture as the premotor cortex. It has major inputs from the basal ganglia via the thalamus, particularly the anterior division of the ventral lateral nucleus and the dorsomedial nucleus. Efferent connections are with the putamen, thalamus, pontine nuclei and spinal cord; there are also widespread reciprocal connections with many cortical regions including M1, and dense callosal connections with the opposite hemisphere (Buser et al., 1992).

Functional imaging studies (Roland et al., 1980) indicate that the SMA is involved in planning and preparation of movement, with similar functions to the PMA; like the PMA, unilateral distal movements result in bilateral activation of this area in functional imaging studies (Roland et al., 1980). However, the SMA appears to be particularly important in planning and initiating well-learned complex motor sequences which do not require sensory information for their execution, wheras the PMA is more important in movements which are based on sensory input (Roland and Zilles, 1996). Electrical stimulation of SMA results in a conscious 'urge to move' followed at higher currents by actual movements (Fried et al., 1991). These movements usually consist of the adoption of proximal, segmental postures which may be unilateral (usually contralateral) or bilateral (Penfield and Welch, 1951). A somatotopic organization of the SMA exists, with the face represented rostrally and the lower limb caudally (Penfield and Welch, 1951; Mitz and Wise, 1987; Fried et al., 1991).

6.2d. Frontal Eye Field

The frontal eye field (FEF) is located on the dorsal convexity of the fontal lobe. It lies anteriorly to the premotor cortex, in the lower part of Brodmann's area 8, principally at the intersection of the precentral and superior frontal sulci. The FEF may also involve part of Brodmann's areas 6 and 9 (Figure 6.2). This area is responsible for the preparation and triggering of voluntary conjugate saccadic eye

movements. It is also involved in pursuit eye movements, in conjunction with the parietal eye field, but is less involved with reflexive saccades triggered by a suddenly appearing peripheral target (Pierrot-Deseilligny et al., 2004).

Electrical stimulation of this area causes conjugate deviation to the opposite side (Blanke and Seeck, 2003). Destructive lesions in this area cause conjugate deviation towards the side of the lesion.

6.2e. Broca's (motor) language area

The language system is complex and a full discussion of its components and organization are beyond the scope of this review. In brief, however, the motor language area occupies the opercular and triangular region of the inferior frontal gyrus, corresponding to Brodmann's areas 44 and 45, on the dominant hemisphere (usually the left). It functions in conjunction with Wernicke's (sensory) language area, which is located in the superior temporal gyrus; the two regions are connected by the arcuate fasciculus. Destruction of any part of the language system results in aphasia; classically destruction of the motor language area results in a non-fluent, expressive aphasia with relatively preserved comprehension.

6.2f. Anterior Cingulate Cortex

The anterior cingulate cortex forms a large region around the rostrum of the corpus callosum. It comprises Brodmann's area 24, and functionally also involves areas 25 and 32 (Devinsky et al., 1995), and is characterized cytoarchitectonically by prominent layer V neurons. It has afferent connections with the anterior, dorsomedial, midline and intralaminar thalamic nuclei; efferent projections are widespread, including the primary motor cortex and striatum. It has prominent reciprocal connections with other parts of the limbic system (particularly the parahippocampal gyrus) through a major association fasciculus, the cingulum.

Functionally, the anterior cingulate cortex is involved with the regulation of autonomic and endocrine functions, as well as being implicated in the control of affect, particularly conditioned emotional learning and vocalizations associated

with expressing internal states. As such, it appears to play a key role in social interactions (Devinsky et al., 1995). Cortical stimulation studies in this region result in autonomic, visceromotor and affective sensations, along with simple or more complex movement patterns; the latter may result from a degree of functional overlap with the SMA (So, 1998). Anterior cingulate lesions result in affective and motor neglect, clinically presenting with apathy, akinetic mutism, or disturbed social behaviour (Devinsky et al., 1995; So, 1998).

6.2g. Prefrontal Cortex

The large region of cortex in the frontal lobes which is not directly associated with motor activity is known as the prefrontal cortex. This region is essentially association cortex, playing an essential role in higher-order cognitive functions, and is highly developed in humans. It is characterized cytoarchitectonically by granular cortex and corresponds to Brodmann's areas 9, 10, 11 and 12. These areas have variations in cytoarchitecture, but it is not possible to ascribe specific functions to any given area (Ramnani and Owen, 2004). Likewise, how exactly the prefrontal cortex achieves its cognitive functions is not understood (Wood and Grafman, 2003). It has wide and extensive connections throughout the brain, both cortically and subcortically. The most prominent subcortical connections with the prefrontal cortex are from the mediodorsal thalamus, which appears to send afferents and receive efferents with all areas of prefrontal cortex (Fuster, 1997). There are also reciprocal connections with the hypothalamus, the mesencephalon and the limbic system. The limbic connections are largely through the uncinate fasciculus, a well defined bundle of nerve fibres between the orbitofrontal cortex and the temporal pole.

Cortically, there are widespread reciprocal connections between areas within the prefrontal cortex and the frontal lobes of both hemispheres. The left and right frontal lobes are connected primarily via the corpus callosum. There are also extensive connections with parietal, occipital and temporal cortex resulting in direct and indirect connections with those areas responsible for somatosensory, visual and auditory processing and memory. These connections are particularly prominent with other areas of association cortex, and their fibres constitute a

number of identifiable white matter tracts. These include the superior and inferior longitudinal fasciculi, and the superior and inferior occipitofrontal fasciculi.

The extensive connectivity of the prefrontal cortex appears to facilitate the access of sensory, spatial, motivational and affective data (both current and remembered) and to use these data in executive and cognitive functioning. Damage to the prefrontal cortex produces a number of neuropsychological deficits attributable to disruption of this system (Fuster, 1997; Stuss and Levine, 2002; Godefroy, 2003); these are interrelated and overlap considerably within individual subjects.

(i) Deficits of attention and perception. These take a variety of forms including distractibility, poor concentration and lowering of general awareness. Neuropsychological assessment of attentional functions may reveal deficits in an individual's ability to switch attention between different tasks, their ability to attend to selective stimuli while ignoring others, and their ability to sustain attention to a given task.

(ii) Memory deficits. Prefrontal cortical function plays an important role in both the retrieval of memory, and the placing of memories in spatial and temporal contexts. Memory disorders, including confabulation and retrograde amnesia, are common sequelae of prefrontal dysfunction.

(iii) Impairment of language. Problems with with impaired activation and formulation of speech and language, may occur with prefrontal cortical dysfunction. These "paralinguistic" disorders reflect truncated spontaneous language, and problems with formulation of sentences and more complex narratives (such as stories).

(iv) Dysfunctional planning and execution. This may take a variety of forms. Individuals may have problems initiating responses and actions, or, conversely, may be unable to suppress inappropriate responses. They may have difficulties with tasks which require problem-solving or the recognition of rules. Finally, the ability to plan or develop strategies is often impaired. As a result of these

problems, individuals may continue to perform old routines without difficulty, but are often unable to plan and initiate new goal-directed patterns of behaviour.

(v) Dysfunctional motility. This may take the form of either reduced spontaneous movement (more prevalent with dorsolateral lesions) or excessive and aimless mobilisation (more often seen with orbitofrontal lesions).

(vi) Disordered emotional and social behaviour. Ventral and polar frontal cortex appears to be vital in these aspects of human personality. Impairment of these regions most commonly manifests with apathy and blunting of emotional response, although occasionally a euphoric or hypomanic state may be seen. The individual often loses basic social decision-making skills, apparently unable to regulate their behaviour according to internal goals and restraints.

These neuropsychological deficits occur to varying degrees in individuals with prefrontal cortex dysfunction. Clinically, they result in a recognizable but heterogeneous entity termed "frontal lobe syndrome" or "dysexecutive syndrome". Features including abulic affect, confabulation, perseveration or stereotyped behaviour, distractibility and disinhibition are key components of this clinical syndrome. Disturbances of emotional, sexual and social behaviour may also be features; when present these are often striking and socially disabling.

Conclusion.

The frontal lobe is the largest lobe in the human brain, and is involved in a variety of functions including motor control, language, emotion and higher cognitive processes. In view of its large size, functional complexity and extensive connectivity, a wide variety of seizure types originating in the frontal lobe might be expected. This is indeed the case, and these will be discussed in the following chapter.

CHAPTER 7

FRONTAL LOBE EPILEPSY
Electroclinical features of Frontal Lobe Seizures

Introduction

Frontal lobe epilepsy (FLE) is the second most common focal epilepsy in large surgical series (Manford, 1996), accounting for about 20% of cases. In contrast to temporal lobe epilepsy, the most common focal epilepsy, seizures arising in the frontal lobes can present with a wide variety of clinical and electrographic features (Williamson and Jobst, 2000). This variability has resulted in a somewhat confusing literature on the subject, which I have addressed here by dividing the chapter into five sections. In the first section, general features of frontal lobe epilepsy are reviewed. In the second, the current ILAE subclassification of FLE is discussed, and in the third section a more practical and frequently used classification is described. The fourth section is a review of possible physiological mechanisms responsible for the nature of frontal lobe automatisms, and the final section comprises a discussion of the electrographic features of FLE.

Section 7.1. Frontal lobe seizure semiology: general features

The recognition of seizure semiology referable to frontal lobe involvement dates from the observations of Penfield and his intracranial stimulation studies of the motor cortex and supplementary motor area (Penfield, 1954). Since then, however, the wide range of seizure types and ictal manifestations referable to the frontal lobes has become increasingly apparent - this is in contrast to seizures of temporal lobe origin which, in general, are broadly similar from patient to patient. The great variability seen in frontal lobe seizures, due at least in part to the functional complexity and extensive connectivity of this region, makes it difficult to describe a 'typical' event. As such, attempts have been made to subdivide frontal lobe seizures on anatomical or semiological grounds, and these will be

discussed later in this chapter. Before considering these, however, the general features of frontal lobe seizures are reviewed.

7.1a. Aura

Auras are relatively common in frontal lobe seizures, although in reported case series of frontal lobe epilepsy the frequency has ranged widely from 11% to 69% (Rasmussen, 1983; Williamson et al., 1985; Salanova et al., 1994; Chauvel, 1995; Jobst et al., 2000; Kotagal et al., 2003). The most common aura is somatosensory, usually a non-specific cephalic sensation but also commonly a feeling in the trunk, limbs, chest or throat (Rasmussen, 1983; Chauvel, 1995; Salanova et al., 1995; Scheffer et al., 1995; Jobst et al., 2000). Autonomic auras, consisting of hot flushes, feelings of difficulty breathing, palpitations or a need to urinate are relatively common, as are emotional auras characterized by feelings of fear or terror (Broglin, 1992; Jobst et al., 2000). Visual auras have been occasionally reported (Williamson et al., 1985; Broglin, 1992; Chauvel, 1995), usually consisting of a non-specific and non-lateralising manifestation such as blurring of vision. Although psychointellectual complaints including the phenomena of "forced thinking", originally described following stimulation of the medial-orbital frontal region (Penfield, 1954), are said to be highly suggestive of frontal lobe origin, they are rarely reported (Broglin, 1992). In general, auras in FLE are relatively non-specific and rarely have clear lateralizing or localizing value (Williamson and Spencer, 1986; Williamson and Jobst, 2000).

7.1b. Vocalisation

Vocalisation is common in FLE, being reported in between 50% and 80% of cases (Williamson et al., 1985; Waterman et al., 1987; Salanova et al., 1995; Jobst et al., 2000). It ranges from simple (moaning, screaming or grunting) to complex (syllables, incomprehensible words or palilalic speech). Speech arrest is well described, particularly in dominant hemisphere seizures involving the supplementary motor area or dorsolateral convexity (Morris et al., 1988; Broglin, 1992; Quesney et al., 1992; Salanova et al., 1995).

7.1c. Motor Activity

The majority of seizures of frontal lobe origin, unlike temporal lobe seizures, have prominent motor manifestations (Waterman et al., 1987; Jobst et al., 2000; Williamson and Jobst, 2000). These may take a number of forms, including tonic posturing, focal clonic activity and agitated gestural and semipurposful automatisms (Waterman et al., 1987; Broglin, 1992; Williamson, 1992; Chauvel, 1995; Salanova et al., 1995; Williamson and Jobst, 2000).

Automatisms. As with vocalisation, motor automatisms range from the simple (such as crossing and uncrossing of the legs or rubbing hands) to the complex and sometimes ambulatory (with running, screaming of obscenities, and complex agitated movements)(Waterman et al., 1987; Williamson and Jobst, 2000). Characteristically, automatisms are bilateral and often have a prominent axial component (Waterman et al., 1987). They are often accompanied by changes in facial expression which may be blank staring, but more commonly are fearful; occasionally smiling and laughter are observed (Chauvel, 1995). Sexual automatisms, including pelvic thrusting and genital manipulation may be seen (Spencer et al., 1983). The automatisms, while highly varied between subjects, are usually stereotyped within a given subject, although sometimes more complex automatisms may adapt to incorporate environmental stimuli (Broglin, 1992).

Postural Manifestations. In some frontal lobe seizures, tonic posturing is the dominant clinical manifestation, and these will be described in more detail below. However, a degree of tonic posturing is common in many frontal lobe seizures, presumably due to involvement of the SMA and PMA (Wieser, 1992).

7.1d. Rapid and frequent secondary generalization.

It is often stated that secondary generalization is both rapid and common in fontal lobe epilepsy (Rasmussen, 1983; Williamson, 1992). Video EEG studies have supported the assertion that secondary generalization, when present, tends to occur more rapidly in frontal lobe epilepsy than in temporal lobe epilepsy (Kotagal et al., 2003). However, some authors have questioned the concept that secondary generalization is particularly common in frontal lobe epilepsy, as it has been an

infrequent finding in some case series (Chauvel, 1995; Jobst et al., 2000; Kotagal et al., 2003).

7.1e. Brief duration.

Unless secondary generalization occurs, frontal lobe seizures are characteristically brief, usually under 1 minute in duration (Williamson et al., 1985; Kotagal et al., 2003).

7.1f. Clustering.

Frontal lobe seizures often occur in clusters or flurries (Waterman et al., 1987; Jobst et al., 2000; Williamson and Jobst, 2000). Patients may have multiple seizures in a period of hours or days; it is not uncommon for a patient to report over thirty seizures in a single day or night (Jobst et al., 2000). Periods of days or weeks with frequent seizures may alternate with longer periods with few or no seizures.

7.1g. Nocturnal predominance.

Many individuals with frontal lobe epilepsy have predominantly nocturnal seizures. The proportion of patients who show this predominance varies between studies, but has been reported in about 35% to 60% of subjects (Crespel et al., 2000; Jobst et al., 2000; Williamson and Jobst, 2000). Some individuals have seizures exclusively or almost exclusively during sleep; this condition is known as nocturnal frontal lobe epilepsy, or NFLE (Meierkord et al., 1992; Provini et al., 1999).

7.1h. Status epilepticus.

Status epilepticus appears to be relatively common in frontal lobe epilepsy (Williamson et al., 1985). Convulsive, complex partial, or focal motor status epilepticus have all been widely reported (Williamson, 1992).

Section 7.2.The ILAE subclassification of frontal lobe seizures

7.2a. Current subclassification and its limitations

In the most recent International League Against Epilepsy classification system (ILAE, 1989), frontal lobe epilepsy is divided into six anatomically and clinically distinct subtypes, the clinical features of which are summarised in Table 1. The utility of this subclassification has, however, been questioned (Manford, 1996). As discussed in Chapter 2, the ILAE sytem classifies seizures on electroclinical grounds, with a combination of seizure semiology and electrographic features being used to determine the epilepsy syndrome. Ultimately, the value of such a system depends upon the reliability of the stated clinical and electrographic features in localizing the site of seizure onset. However, the extensive anatomical connections within the frontal lobes (and between the frontal lobes and other cortical and subcortical regions), results in extremely rapid seizure propagation, within milliseconds; in addition, many areas in the frontal lobes are clinically 'silent'. As a result, the clinical features observed in frontal lobe seizures often arise through the involvement of regions distant from the site of origin. Seizures rarely remain restricted to one subregion of the frontal lobe (Chauvel, 1992; Manford, 1996), and this produces considerable overlap between seizure types seen from different regions. In many cases it is impossible to locate the true site of seizure origin (Williamson, 1992).

7.2b. Methodological considerations

Examination of the methodology used to develop the subclassification reveals the reasons for its limitations. The system was drawn up in the pre-MRI era, and is based on data of two types. The first is 'pure cultures' of patients with frontal lobe epilepsy, in whom seizure localization has been confirmed by post-surgical remission (Rasmussen, 1983; Quesney et al., 1992; Smith et al., 2004), in conjunction with data from intracranial and scalp EEG. In other words, the classification is based on a group of patients who have been fully assessed for surgery, have undergone a surgical resection of a region of the frontal lobe, and have been rendered seizure free by their procedure. While this methodology

Anatomical region	Principal clinical manifestations
Supplementary Motor Area	Postural, simple focal tonic seizures with vocalization, speech arrest and fencing, or complex focal with urinary incontinence. Ictal EEG shows flattening, rhythmic polyspikes, and secondary generalization.
Cingulate	Complex focal seizures, with sexual automatisms, vegetative signs, affective changes and urinary incontinence. Depth electrode exploration is mandatory for detection of the seizure focus.
Anterior (polar) frontal region	Loss of contact, adversive and subsequent contraversive movements of head and eyes, axial clonic jerks and falls, and autonomic signs. Frequent evolution to GTCS.
Orbitofrontal	Complex focal with automatisms, olfactory hallucinations, autonomic signs and urination. The EEG shows flattening, rhythmic polyspikes and secondary generalization. Nasoethmoidal and orbital electrodes may be helpful.
Dorsolateral	Simple focal tonic with versive movements and aphasia, or complex focal with automatisms. The EEG focus is usually detected by scalp EEG.
Motor cortex	Mainly simple partial seizures with Jacksonian march; the exact symptoms depend on the side and topography of the area involved.

Table 7. 1 *The ILAE subclassification of frontal lobe seizures*

represents the gold standard for localization of the epileptic focus, there are relatively small numbers of such patients reported in the literature. Frontal lobe epilepsy is highly variable in its clinical presentation, and validity of extrapolating the findings from small, selected samples of individuals to the broader patient population is questionable. This is particularly true when so little data is published describing the electroclinical features in the 60-80% of individuals undergoing frontal lobe epilepsy surgery who showed little or no improvement (Rasmussen, 1991).

The second type of data is that arising from patients with frontal lobe epilepsy who have undergone monitoring with scalp or implanted intracranial electrodes (Tharp, 1972; Waterman et al., 1987; Morris et al., 1988; Munari, 1992). Unfortunately, this technique is fraught with difficulties in frontal lobe epilepsy (Williamson, 1992). This is mainly due to two factors: firstly, the very large surface area of the frontal lobes, which makes complete coverage of the region with electrodes or even subdural grids impossible; and secondly the extremely rapid spread of seizures in the frontal lobes, such that electrical onset may appear almost instantaneously in several brain regions (Veilleux et al., 1992; Williamson, 1992). As a result, intracranial EEG monitoring of frontal lobe epilepsy is prone to sampling error, in which the area of seizure onset is not directly sampled by the implanted electrodes. Sampling error may result in negative findings, in which widespread ictal rhythms with no clear localization are obtained; it may also result in 'false positive' findings, in which an area of seizure propagation is sampled but the true area of ictal onset is not. This gives an appearance of seizures onset from the site of propagation and is therefore falsely localising. For example, a patient may have seizures characterized by asymmetric tonic posturing, which in fact are originating from a clinically silent region of prefrontal cortex but rapidly propagating to the SMA. If the relevant area of prefrontal cortex is not sampled but the SMA is, false localization to the SMA may occur.

Since the current classification system was developed, it has become apparent that the ILAE subclassification is indeed overly proscriptive. Rapid advances in neuroimaging have enormously improved the ability of clinicians to localize epileptogenic lesions *in vivo,* and the widespread availability of video EEG

monitoring has enabled the study of large numbers of patients with frontal lobe epilepsy. These advances have highlighted the great variability of this condition and the inconsistent relationship of seizure semiology to the site of ictal onset (Manford, 1996).

Section 7.3. Practical categorisation of frontal lobe seizures

Although the ILAE classification has not yet been revised, it is practically more useful to categorize frontal lobe seizures on the basis of seizure semiology. The three main types of seizure described are the supplementary motor area (SMA) seizure, the focal motor clonic seizure, and the frontal lobe complex partial seizure (FLCPS) (Salanova et al., 1995; Williamson and Jobst, 2000). Further subtypes have been described, and these will be also be discussed briefly. These seizure types are descriptive and do not imply a specific site of seizure origin.

7.3a. SMA seizures

The effects of electrical stimulation of the Supplementary Motor Area (SMA) in humans were first described by Penfield and his co-workers, who demonstrated that stimulation of this region elicited complex postures (the 'fencing posture') and speech disturbance (Penfield and Welch, 1951; Penfield, 1954). SMA seizures were subsequently described by Ajmone-Marsan and Ralston (Ajmone-Marsan, 1957), who termed the characteristic asymmetric tonic posturing the 'M2e posture'.

Since that time, particularly in the 1980s and 1990s, extensive studies of SMA seizures have been undertaken using video monitoring and scalp or implanted intracranial electrodes (Morris et al., 1988; Veilleux et al., 1992; So, 1998). Typically, an SMA seizure will start with the sudden, often explosive, adoption of an asymmetric tonic posture. There is deviation of the head and eyes contralaterally to the EEG focus, accompanied by abduction and external rotation of the contralateral arm at the shoulder with elbow flexion such that the patient appears to be looking at his upraised hand. The tonic posturing may involve one or more limbs, and all four limbs may be affected (Morris et al., 1988); if the

ipsilateral arm is involved it is often flexed (Williamson, 1992). In addition to this characteristic posture, a number of other features may be present. It may be preceded by a somatosensory aura, either a pulling, heavy sensation, or occasionally numbness and tingling (Salanova et al., 1995; Williamson and Jobst, 2000). Arrest of speech is common, but in some patients speech is unaffected and the patient may utter coherent words. More commonly, inarticulate groaning or grunting is heard. Consciousness is characteristically retained during the seizure. The seizures are usually frequent, occurring in clusters, and arising primarily from sleep (Waterman et al., 1987).

It should be noted that although involvement of the SMA is assumed in seizures of this type, they are by no means pathognemonic of seizure *onset* in this region. Onset may be elsewhere within or even outside the frontal lobes but present in this fashion due to the extensive connectivity of the region.

7.3b. Focal clonic motor seizures

Although SMA seizures were described half a century ago, focal clonic motor seizures have been recognised since antiquity (Temkin, 1994). They were first carefully studied by Bravais and Herpin in the 19th Century (Loiseau, 1992), but it is John Hughlings Jackson's influential clinical and theoretical studies later in that century that are most widely associated with this seizure type (Jackson, 1958). As a result of his insights, supported by Penfield's identification of the human motor homunculus in the precentral gyrus (Penfield, 1954), focal clonic seizures have become almost synonymous with primary motor cortex onset. However, as with other seizure types, it is now recognized such seizures may originate elsewhere in the brain, with the clinical manifestations reflecting propagation to eloquent cortex.

Two broad subtypes of focal clonic motor seizure are recognized: the *Jacksonian March* and *epilepsy partialis continua.*

Jacksonian March. The primary manifestation of this seizure type is clonic jerking of one side of the body, contralateral to the site of seizure origin. Onset

may be in any muscle group, but is most common in those areas which have larger cortical representations on the motor homunculus of the primary motor cortex. Therefore, if starting in the face, it will often begin in the mouth, as this has a large cortical representation; likewise, in the upper limb it will usually start in the hand, often the thumb or index finger, and in the lower limb it will begin in the foot, often in the great toe (Jackson, 1958). Clinically the seizure may spread at a variable rate, and as noted in Jackson's original writings "The point of great interest is the march of the spasm. Fits beginning in the foot have a different march from those beginning in the hand, although in each the same muscles are ultimately convulsed. When a fit begins in the hand, it goes *up* the arm and *down* the leg. Now patients who have fits beginning in the foot tell me the spasm goes up the leg and down the arm" (Jackson, 1958). This sequence reflects the progressive spread of the seizure through motor cortex. In addition to the clonic jerking, unilateral tonic posturing of the affected limbs is very common during these seizures, with abduction, elevation or flexion of either limb often observed (Chauvel, 1992). Head and eye version may be seen, but is not common, and may be either contralateral to the seizure focus or ipsilateral, apparently reflecting propagation of the seizure to the opposite hemisphere (Chauvel, 1992). Consciousness is preserved. Clinically, the seizures may remain restricted to this pattern, or may spread. Sensory symptoms, such as tingling or numbness, are common and indicate involvement of the primary sensory cortex located in the post central gyrus (Bancaud, 1992; Chauvel, 1992); bilateral asymmetric tonic posturing (presumably due to the involvement of SMA) may be seen (Chauvel, 1992; Salanova et al., 1995) often immediately prior to secondary generalization (Lehman et al., 1994).

Although focal clonic motor activity is a reliable *lateralizing* sign, indicating seizure onset in the contralateral hemisphere (Salanova et al., 1995; Jobst et al., 2000), its *localizing* value is limited. As with SMA seizures, extensive connectivity in the region results in rapid seizure propagation; while therefore implies involvement of the primary motor cortex in the seizure, it does not necessarily follow that it is the site of seizure origin. Even when focal clonic activity is the only clinical manifestation, true seizure onset may be located in a

clinically 'silent' area elsewhere within, or even outside, the frontal lobes (Williamson and Jobst, 2000).

Epilepsia Partialis Continua (EPC). This represents a specific form of focal motor seizure, characterized by continuous focal myoclonus which was first described by Kojewnikow (Kojewnikow, 1895). It has been defined as "spontaneous regular or irregular clonic twitching of cerebral cortical origin, sometimes aggravated by action or sensory stimuli, confined to one part of the body, and continuing for a period of hours, days or weeks" (Obeso, 1985). EPC differs from Jacksonian seizures in three major ways: firstly, it does not have a general tendency to spread or 'march' (although Jacksonian seizures may evolve from EPC); secondly, it does not stop after the usual time course of focal motor seizures; and finally it is highly refractory to treatment with antiepileptic drugs (Bien et al., 2005). The exact nature and origin of EPC was the subject of considerable debate for many years, but data from implanted depth electrodes in patients being considered for surgery have now confirmed that EPC represents a form of focal motor status epilepticus (Wieser, 1977; Chauvel, 1992). It is most commonly associated with an underlying structural lesion such as stroke, tumour or arteriovenous malformation (Cockerell et al., 1996). Rasmussen's encephalitis, a rare immune-mediated brain disorder that causes unilateral hemispheric atrophy, is classically associated with EPC and is the most common cause of this condition in children (Cockerell et al., 1996; Bien et al., 2005).

7.3c Frontal Lobe Complex Partial Seizures

Frontal lobe seizures with unusual behavioural manifestations were described in the 1970s and earlier (Geier et al., 1976; Geier et al., 1977), but since the widespread availablility of video EEG technology Frontal Lobe Complex Partial Seizures (FLCPS) have been extensively studied and the key features more clearly defined (Williamson et al., 1985; Waterman et al., 1987; Wieser, 1992; Chauvel, 1995). As discussed previously, they may begin with an aura, most commonly a somatosensory sensation but with affective or autonomic features also often reported. The seizures are then characterized by the explosive onset of prominent motor automatisms, which usually have an agitated appearance. The

activities seen include prominent bimanual and bipedal movements, such as cycling or kicking movements of the legs, hand clapping and leg slapping. Axial movements, such as rocking, thrashing, running (often in an apparently agitated or distressed manner), sitting up and head nodding are common. In some patients automatisms have a semipurposeful quality (Chauvel, 1995), and sexual automatisms, including pelvic thrusting and genital manipulation, are sometimes observed (Spencer et al., 1983). Vocalization is common, and often consists of unintelligible screaming or moaning. In some individuals palilalic speech or the screaming of obscenities is seen; others breath deeply or eccentrically but without actual vocalization (Waterman et al., 1987; Chauvel, 1995).

FLCPS tend to be brief and frequent, and occur in clusters with a nocturnal preponderance (Waterman et al., 1987; Crespel et al., 2000; Williamson and Jobst, 2000). Their onset is usually explosive, and offset is abrupt, often with no apparent post-ictal state. During the episode, consciousness may be entirely or partially retained. The subject often describes being aware of his surroundings during the event but without control over his actions and unable to respond (Williamson et al., 1985; Waterman et al., 1987; Williamson, 1995).

7.3d. Other types of frontal lobe seizure

Seizures resembling temporal lobe seizures. Frontal lobe seizures may present with features very similar to those seen in temporal lobe epilepsy, with arrest of activity, unresponsiveness and oroalimentary automatisms; they may also be associated with electroencephalographic features of temporal lobe epilepsy (Williamson and Jobst, 2000). In some such cases the site of origin has been localized to the orbitofrontal region (Munari, 1992; Smith et al., 2004). Intracranial studies have suggested that the orbitofrontal area itself results in very few clinical manifestations, and that the seizure semiology in these cases is a result of rapid propagation to adjacent areas (Munari, 1992). In some cases this will be the temporal lobe, but spread to other regions in the frontal lobes may also occur, resulting in more dramatic presentations (Tharp, 1972; Bancaud, 1992; Munari, 1992).

Frontal Lobe 'Absences'. Seizures clinically resembling absences have been reported in patients with frontal lobe epilepsy; these patients may also have generalized tonic-clonic seizures, giving a clinical picture similar to idiopathic generalized epilepsy (Bancaud, 1992). Occasionally these are associated with 3Hz spike wave patterns, giving an appearance similar to true absence seizures, although the spike-wave activity is usually more irregular and at a slower frequency than idiopathic generalized epilepsy (Bancaud, 1992; Chauvel, 1995). In other cases a more disorganized, diffuse EEG has been described (Williamson and Jobst, 2000).

Section 7.4. Interpretation of automatisms in FLE

The main types of frontal lobe seizure described (SMA seizure, focal clonic motor seizure, and frontal lobe complex partial seizure, FLCPS) appear to have fundamentally different mechanisms. The 'Jacksonian march' is clearly referable to a cortical structure, the motor homunculus of the precentral gyrus; similarly, the asymmetric tonic posturing of SMA seizures appears to have a clear relationship to a region of frontal cortex, as demonstrated by the electrical stimulation studies of Penfield (Penfield and Welch, 1951). However, the bizarre and dramatic automatisms of FLCPS are more difficult to explain. Such automatisms have not been elicited by way of direct cortical stimulation, and it is conceptually difficult to link the range of dramatic, emotional and sometimes violent behaviours to a specific region of frontal lobe cortex (Tinuper et al., 2005).

Some authors have speculated that these automatisms reflect innate behavioural patterns which are released from inhibition by the focal seizure (Tassinari et al., 2005). These authors hypothesise that such behaviours, being fundamental and phylogenetically primitive survival behaviours, are encoded in subcortical neural networks known as central pattern generators (CPGs), and are released from higher inhibition by the seizure. CPGs are well recognized in basic neuroscience. They comprise neural networks in the spinal cord, brainstem and other subcortical regions, which are responsible for basic innate behaviours such as locomotion (Grillner and Wallen, 1985). At the present time, study of CPGs has been largely

restricted to mechanisms for walking and swimming in simple lizards and amphibians. However, similar patterns are thought to exist in all animals, and it is widely believed that they are also responsible for more complex behaviours such as emotional expression and feeding (Grillner, 2003; Kiehn, 2006). The negative emotional facial expressions, vocalization, and ambulatory automatisms prominent in FLCPS have been interpreted by some authors as a release from inhibition of fundamental survival behaviours encoded in subcortical CPGs (Tassinari et al., 2003; Bartolomei et al., 2005; Tassinari et al., 2005); indeed, these authors speculate that other automatisms, such as chewing and lip smacking in temporal lobe epilepsy, may reflect similar phenomena (Meletti et al., 2004).

Section 7.5. Electroencephalographic findings

7.5a. Interictal EEG

The interictal scalp EEG in frontal lobe epilepsy can be difficult to interpret. In temporal lobe epilepsy, interictal and ictal discharges have a relatively high localizing and lateralizing value (Blume et al., 2001; Foldvary et al., 2001). This is not the case in frontal lobe epilepsy, particularly when the epileptic focus lies on the medial aspect of the frontal lobes (Williamson, 1995; Vadlamudi et al., 2004). In a significant proportion of these cases no interictal epileptiform discharges are seen. The EEG may be entirely unremarkable, or may show only non-specific abnormalities such as bilateral or midline theta slowing (Morris et al., 1988). When interictal epileptiform discharges are present, they are often of limited lateralizing or localizing value, being located only in the midline or diffusely over both frontal regions. (Williamson et al., 1985; Waterman et al., 1987; Morris et al., 1988; Bautista, 1998). Occasionally a 'secondary bilateral synchrony' pattern is seen. This was first described in patients with parasaggital lesions (Tukel, 1952) and consists of bilateral spike and wave discharges. While there may be similarities with the generalized spike-wave pattern seen in idiopathic generalized epilepsy, the activity is usually more irregular and of a lower frequency. This finding has been reported frequently since the initial observation (Williamson, 1992), and has also been associated with seizures of cingulate origin (Mazars, 1970).

Focal and lateralizing EEG discharges are more frequently seen if the epileptic focus lies on the dorsolateral convexity than the medial structures (Bautista, 1998; Vadlamudi et al., 2004), but even in these cases they tend to be regional than highly focal (Quesney, 1992). The findings depend, at least in part, on the nature and extent of the epileptic focus. A spectrum of interictal patterns, ranging from a normal interictal EEG to continuous focal or regional spiking, has been reported in these patients (Niedermeyer and Lopes de Silva, 2004).

7.5b Ictal EEG

In general, the ictal EEG patterns of frontal lobe seizures are broadly similar to those of other neocortical epilepsies (Niedermeyer and Lopes de Silva, 2004). As with interictal EEG, the problem is one of sampling; the medial and inferior aspects of the frontal lobes are not directly accessible using scalp EEG monitoring. While in some patients, generally those with a seizure focus on the dorsolateral convexity, ictal scalp EEG may be informative (Williamson and Spencer, 1986), more often the patterns seen are unhelpful. Many frontal lobe seizures, particularly those arising from medial frontal foci, are associated with little or no change in the EEG, and subtle changes may be obscured by muscle and movement artifact from prominent motor activity (Williamson, 1992; Salanova et al., 1995; Bautista, 1998). Other seizures are associated with non-specific electrographic changes such as attenuation of background rhythms or diffuse postictal slowing, without clear ictal rhythms (Morris et al., 1988). As a result, many subjects with frontal lobe epilepsy may be incorrectly diagnosed with pseudoseizures or other non-epileptic events (Morris et al., 1988; Kanner, 1990).

When ictal rhythms are present on the scalp EEG, the must be interpreted with caution as they may be misleading. Rapid propagation from mesial foci to the dorsolateral convexity can give a misleading impression of the site of seizure origin (Veilleux et al., 1992). In other cases frontal lobe seizures, particularly those arising in the orbitofrontal region, can be associated with interictal and ictal scalp EEG changes suggestive of a temporal focus (Williamson and Spencer, 1986).

7.5c. Intracranial EEG.

As stated previously, although clinical seizure patterns have been associated with involvement of SMA and primary motor cortex, there is ample evidence that such seizures may originate elsewhere within or even outside the frontal lobes and rapidly propagate to these regions (Williamson, 1992; Salanova et al., 1995; Manford, 1996; Jobst et al., 2000). Aspects of semiology such as tonic posturing or clonic jerking may be useful in lateralizing ictal onset (Bleasel et al., 1997; Werhahn et al., 2000), but are of limited value in accurate localization. Likewise, scalp EEG is often of limited value for the reasons discussed in this section. Monitoring with intracranial electrodes is usually mandatory when surgery is considered in such cases but, due to the limited area of brain tissue that may be sampled by this technique, is susceptible to the problems with sampling error. Careful analysis of all data, including clinical history, ictal semiology, scalp EEG and imaging findings must be performed when planning the implantation strategy in such patients.

Summary

Although seizures of frontal lobe origin may present with a wide variety of clinical manifestations, a number of common features such as prominent motor activity, clustering and nocturnal predominance have been identified. Attempts to attribute various clinical features of these seizures to specific regions within the frontal lobes have, however, been largely unsuccessful. While some features appear to be associated with involvement of specific cortical regions (such as asymmetric tonic posturing with SMA involvement), the large area of clinically 'silent' cortex in the frontal lobes, coupled with the extensive connectivity in this region, makes accurate localization of seizure onset on clinical grounds almost impossible.

Seizures are best considered as either focal motor seizures, SMA seizures or complex partial seizures. These seizure types, while implying involvement of certain areas within the frontal lobes, are semiological categories and do not provide implicit information as to the site of seizure origin.

The inaccessibility of large areas of the frontal lobes to scalp EEG makes electrographic localization of seizure onset problematic, even with intracranial monitoring, and many frontal lobe seizures are associated with a normal EEG or only non-specific changes. When attempting to identify the site of seizure onset it is of paramount importance that all available data, including clinical history, seizure semiology, electrographic changes and imaging findings are utilized. Even when this occurs, in many cases of frontal lobe epilepsy accurate localization is not possible.

CHAPTER 8

FRONTAL LOBE EPILEPSY
Nocturnal Paroxysmal Dystonia and Nocturnal Frontal Lobe Epilepsy

Introduction

It has been recognized for some time that frontal lobe seizures have a predilection to occur during sleep. However, as a result of the unusual seizure manifestations and the frequently unhelpful EEG findings, an appreciation of the full range of FLE presentations was slow to emerge. In particular, frontal lobe seizures restricted to sleep caused, and continue to cause, considerable diagnostic difficulty. In this chapter, the recognition of nocturnal frontal lobe epilepsy (NFLE) as a distinct clinical entity is discussed, and the clinical features of this condition are described.

Section 8.1. Development of concepts

8.1a. Nocturnal Paroxysmal Dystonia

In 1981, five patients with frequent sleep-related events were reported by Lugaresi and Cirignotta (Lugaresi and Cirignotta, 1981). These individuals had frequent steroptyped events, occurring almost every night, characterized by tonic and dystonic posturing and coarse, violent movements. The episodes all arose from stage 2 sleep, were not associated with epileptiform abnormalities on EEG, and were responsive to carbamazepine. Lugaresi and Cirignotta named this condition hypnogenic paroxysmal dystonia, and suggested three possible underlying mechanisms. They suggested that the movements could be a form of sleep terror (i.e. a benign parasomnia), a form of paroxysmal dystonia triggered by arousal from sleep (i.e. a movement disorder), or a form of epilepsy arising from deep or mesial structures.

Over the next decade, further reports of this condition appeared in the literature (Godbout et al., 1985; Lugaresi et al., 1986; Lehkuniec et al., 1988; Maccario and

Lustman, 1990). Whilst evidence for an epileptic basis was seen in some cases, in others the association with the subsequent development of Huntingdon's disease (Lugaresi et al., 1986) concurrent reflex dystonia (Lehkuniec et al., 1988) suggested that the NPD was in fact a movement disorder . It was hypothesized, therefore, that the condition was heterogeneous, and included paroxysmal disorders with different underlying aetiologies. In general, brief attacks (which tended to be more responsive to anticonvulsants) were held to be epileptic in origin, wheras the rarer longer attacks (many of which did not respond to anticonvulsants) were thought to represent extrapyramidal disturbances (Tinuper, 2002). The condition became widely known as nocturnal paroxysmal dystonia (NPD).

At this time, reports were also emerging of patients with multiple, very brief, arousals from NREM sleep. These arousals caused significant sleep fragmentation and daytime somnolence, and in some cases appeared to have an epileptic basis (Peled and Lavie, 1986; Montagna et al., 1990). In addition, the phenomenon of episodic nocturnal wanderings was described (Pedley and Guilleminault, 1977; Maselli et al., 1988) characterized by episodes of vocalization, complex and sometimes violent automatisms, and ambulation.

8.1b. Nocturnal Frontal Lobe Epilepsy

The nature of these episodes, particularly NPD, was widely debated (Lee et al., 1985; Berger et al., 1987), but as more work was performed on the semiology of frontal lobe epilepsy, the similarities between NPD and frontal lobe seizures became apparent. Both conditions presented with prominent tonic and dystonic features or bizarre automatisms, were often associated with preservation of consciousness, and frequently had no associated ictal EEG changes (Rasmussen, 1983; Spencer et al., 1983; Williamson et al., 1985; Waterman et al., 1987; Morris et al., 1988). The tendency of frontal lobe seizures to occur in sleep was also recognized. These striking similarities, combined with the presence of definite epileptiform discharges in a number of NPD patients, resulted in the appreciation that most (if not all) NPD cases were epileptic in origin (Tinuper et al., 1990;

Meierkord et al., 1992), and the term 'nocturnal frontal lobe epilepsy' (NFLE) was coined.

8.1c. Autosomal Dominant Nocturnal Frontal Lobe Epilepsy

It was noticed by some clinicians that a number of individuals with NFLE had a family history of similar sleep related events. In 1994, Scheffer et al described a group of families from Australia, Canada and the UK in whom NFLE was inherited in an autosomal dominant fashion, thus describing autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE) (Scheffer et al., 1994). A genetic mutation was subsequently identified in a nicotinic acetylcholine subunit gene in one of these family (Steinlein et al., 1995), making ADNFLE the first form of human epilepsy for which the fundamental genetic basis had been established . ADNFLE will be considered in detail in Chapter 9.

Section 8.2. Semiological considerations

8.2a. Seizure types in NFLE

Once an epileptic basis to NFLE had been identified, the Bologna group undertook painstaking studies of the semiologic spectrum of this condition. They grouped the seizures of NFLE into three major types, based on their semiology and duration: paroxysmal arousals, lasting 20 seconds or less; paroxysmal nocturnal dystonia, lasting up to 2 minutes; and epileptic nocturnal wanderings, lasting up to 3 minutes (Montagna, 1992). Patients rarely had only a single type of attack; the brief paroxysmal arousals were conceptualized as fragments of larger seizures (Provini et al., 1999), and all events were considered to be manifestations of the same underlying epileptic process.

Paroxysmal arousals consist of abrupt arousal from sleep with vocalization and highly stereotyped motor activity, often consisting of head movements, frightened expressions, and dystonic posturing of the limbs (Provini et al., 2000). They occur repetitively and very frequently throughout the night, often with a periodic repetition (Provini et al., 1999) and are often under-reported. Some individuals

are completely unaware of them and present with excessive daytime somnolence (Peled and Lavie, 1986).

Nocturnal paroxysmal dystonia seizures begin as a paroxysmal arousal, but are subsequently associated with more complex movements including bipedal automatisms, rhythmic twisting movements of the trunk and pelvis, vocalization and tonic or dystonic posturing (Provini et al., 2000).

Episodic nocturnal wanderings usually begin as a paroxysmal arousal, progressing through the nocturnal paroxysmal dystonia stage, followed by jumping from the bed and ambulation (usually in an agitated fashion), screaming or other vocalisation, and sometimes semipurposeful automatisms which may be violent (Maselli et al., 1988; Plazzi et al., 1995). Such episodes are infrequent, with paroxysmal arousals and nocturnal paroxysmal dystonia making up the majority of events in any given individual (Provini et al., 2000).

8.2b. Clinical and electrographic features of NFLE

The definitive study of the clinical features of NFLE was published by the same group at the end of the last century (Provini et al., 1999). They reviewed video EEG and PSG monitoring of one hundred patients with NFLE, examining a total of 660 seizures. A number of key findings arose from this study.

Patients had a mean age of onset of 14 years, but with a very wide range (1 to 64 years). They reported a mean of 20 seizures per month, with one to twenty occurring per night. Most had no identifiable triggers for their seizures. From the history, one third of patients had occasional daytime seizures, and 28% had occasional secondarily generalized tonic clonic seizures. Interestingly, a large number had a personal or family history of events which, from the clinical description, were consistent with typical parasomnias such as sleep walking and sleep terrors. While some patients complained of sleep disturbance, over 70% were unaware of their events and the problem was reported by relatives. Neurological examination was normal in 92%, and neuroradiological examination (with CT or MRI) was normal in 86%.

In terms of ictal semiology, by far the most common seizure type was the paroxysmal arousal, constituting 75% of the recorded seizures; paroxysmal nocturnal dystonia constituted a further 23%, with epileptic nocturnal wanderings making up only 2% of recorded seizures. Most patients had at least two of these seizure types identifiable on monitoring, and autonomic features such as tachycardia and irregular respiration were prominent.

Electrographically, almost all the events occurred during NREM sleep, with about 70% occurring in stage 1 or 2. Interictal EEG was normal in the majority of patients, with only 33% showing clear-cut epileptiform discharges in wakefulness and 45% in sleep. Ictal EEG showed no epileptiform activity in 44%, and in the majority of the remainder focal attenuation or rhythmic theta or delta was the prominent rhythm; only 8% showed spike and wave activity, and another 8% showed focal fast activity.

Conclusion

NFLE is a relatively uncommon and recently recognized form of epilepsy. Major semiological studies of this condition have led to a wider appreciation of its most important clinical features, although accurate diagnosis can still be difficult in clinical practice. While NFLE is not a common disorder, major scientific advances have resulted from its identification (and in particular the familial form ADNFLE) which are likely to have implications for other forms of epilepsy. Further understanding of this condition, both in terms of the clinical features and the genetic basis, is still necessary.

CHAPTER 9

FRONTAL LOBE EPILEPSY
Pathology and Clinical Genetics

Introduction.

The range of pathologic substrates associated with frontal lobe epilepsy (FLE) must be considered in any discussion of this condition. Partial epilepsies tend to be associated with a variety of underlying pathologies, and FLE is no exception. However, Autosomal Dominant Nocturnal Frontal Lobe Epilepsy (ADNFLE), a form of FLE with an established genetic basis, deserves particular consideration. The discovery of this disorder, and the genetic mutations which cause it, has transformed our appreciation of the role played by genetic factors in epilepsy.

In the first section of this chapter the pathological basis of FLE is reviewed, along with neuroimaging correlates. The second secection is a discussion of the clinical and molecular genetics of ADNFLE.

Section 9.1. Pathology and neuroimaging in FLE: general

9.1a. Pathological basis of FLE

With the exception of ADNFLE, an idiopathic partial epilepsy, FLE is usually classified as a symptomatic or cryptogenic partial epilepsy. Accordingly, it has a similar range of underlying pathologies to other symptomatic partial epilepsies. These include congenital abnormalities (such as malformations of cortical development, vascular malformations and developmental tumours), and acquired insults (including neoplasms, CNS infections, vascular insults, head injury and perinatal injury) (Foldvary, 2001).

Most work addressing the pathological basis of FLE has examined post-surgical data. Several FLE series of this nature have been presented, with broadly similar findings. The most widely cited is from the Montreal Neurological Institute, and comprises pathological data from 40 'pure' frontal lobe epilepsy patients

(Rasmussen, 1983); this series was subsequently extended to 187 cases (Robitaille et al., 1992). Tumours and vascular malformations were excluded from these series, in which the most common underlying pathology was *meningocerebral cicatrix* (essentially scarring involving the meninges and cerebral cortex), which accounted for 50% and 33% of cases respectively in the two series). Other common pathological findings were *gliosis* (33% in both series) and *cortical dysgenesis* (7.5% and 15.5%). The cause of the acquired lesions observed in these series was not discussed in detail, although trauma in general was said to account for 50% of cases and birth trauma was the 'presumed' aetiology in 7.5%.

In an earlier large series of surgically treated FLE reported by the same group, a comparable range of aetiologies was identified (Rasmussen, 1963): Head injury (31%), tumour (25%) and birth trauma (10%) constituted the majority of cases, with the remainder attributed to gliosis (secondary to abcess, haematoma etc.; 6%), encephalitis (5%), gunshot (4%) and other known pathology (8%). No pathology was identified in 11% of cases in this series. Another major series of 100 surgically treated cases of FLE from Paris identified neonatal anoxia, head trauma and encephalitis as the most common pathological lesions; only 7% had an underlying tumour and in 37% the cause was unknown after surgery (Talairach et al., 1992).

While these surgical series provide important insights into the pathological basis of FLE, their applicability to FLE in general is unclear. There are several reasons for this. Firstly, these series included a significant number of veterans from the Second World War. While frontal lobe injury is a recognised risk factor for the development of post-traumatic epilepsy (Frey, 2003), it is probably less prevalent in comtemporary society than in these series. Secondly, improvements in neuroimaging over the last decade or so have resulted in increased detection of focal cortical dysplasia and other malformations of cortical development in refractory focal epilepsies, including FLE (Taylor et al., 1971; Chung et al., 2005; Kakita et al., 2005). These abnormalities are almost certainly responsible for more than 7-15% of FLE as reported in the Montreal series. More recent, although smaller, neurosurgical series of frontal lobe epilepsy report malformations of

cortical development in between 26% and 76% of cases (Kim et al., 2002; Schramm et al., 2002); furthermore, cortical dysplasia may be the responsible lesion in a significant proportion of 'lesion-negative' cases (Palmini et al., 2004), many of whom are not considered for surgery. Thirdly, in these series the ascertainment of cases may have been biased towards those individuals with secondarily generalized seizures. As discussed in Chapter 7, the spectrum of frontal lobe seizures was not fully appreciated at the time these series were compiled; many patients with FLE without generalized tonic-clonic seizures may have been misdiagnosed with pseudoseizures or parasomnias and not considered for surgical treatment. Finally, these series take no account of genetic factors in FLE. Until the relatively recent descriptions of familial frontal and temporal lobe epilepsy syndromes, partial epilepsies persisting into adulthood were assumed to be symptomatic in nature. However, it is increasingly apparent that genetic mutations can be responsible for a number of focal epilepsies, including frontal lobe epilepsy. While at present a clear genetic basis to frontal lobe epilepsy is only apparent in a small minority of patients, it is possible that the influence of genetic factors in non-familial FLE is greater than is currently appreciated.

9.1b. Structural imaging in FLE

Magnetic resonance imaging (MRI) is well established as the most sensitive and specific neuroimaging technique in all partial epilepsies, including frontal lobe epilepsy (Bergen, 1989; Cascino, 1991; Kuzniecky et al., 1993). Its effectiveness has been established in the detection of a range of epileptogenic pathologies: malformations of cortical development, post-traumatic gliosis, infection-related changes, and tumours (the most common underlying pathologies from surgical series in FLE) may be detected with high diagnostic yields (Bergen et al., 1989; Palmini et al., 1991; Cascino et al., 1992; Kuzniecky et al., 1993). In particular, the importance of focal cortical dysplasia (FCD) in intractable focal epilepsy has only become apparent since the advent of MRI; this pathology is rarely visible using older imaging modalities such as CT. Type 2, or 'Taylor type', dysplasia (with dysplastic neurons and /or balloon cells) is usually, although not invariably, visible on MRI. Cortical thickening (Chan et al., 1998), blurring of the grey/white interface (Chan et al., 1998; Lee et al., 1998), and increased signal on T2 or

FLAIR sequences (Bronen et al., 1997; Lee et al., 1998) are the typical MRI findings. In contrast, Type 1 FCD (defined as dysplastic cortex without dysmorphic or balloon cells) is not always detectable, although clarification of diagnostic yields of MRI is still unclear in this setting (Palmini et al., 2004).

The ability to detect and delineate epileptogenic lesions is of both practical and academic importance. Epilepsy surgery in FLE has a substantially greater success rate in patients with preoperatively recognized lesions, with an excellent outcome obtained in 72% of individuals with a concordant lesion versus 41% in those with no detectable MRI abnormality (Mosewich, 2000). The overall diagnostic yield of MRI from presurgical series in FLE is quoted at 45 - 60% (Swartz, 1989; Cascino, 1992; Mosewich, 2000); the most recent series have recorded highest yields, presumably a result of technical MRI improvements and increased familiarity with subtle abnormalities.

9.1c. Functional imaging in FLE

Although structural neuroimaging using MRI is the principle technique employed in the evaluation of patients with partial epilepsy, the usefulness of ^{18}F-FDG PET and ictal single-photon emission computed tomography (SPECT) has also been established, particularly in the presurgical setting.

Positron Emission Tomography (PET). As discussed in Chapter 3, PET is based upon computerized reconstruction of images based on the distribution of radioactive tracers in the brain. A wide number of radioactive tracers have been developed for use in PET, allowing measurement of glucose metabolism, blood flow or receptor density for specific neurotransmitters. The bulk of experience in epilepsy is with ^{18}F-FDG PET, which measures glucose metabolism. Characteristically, reduced metabolic activity is observed around the epileptic focus (Kuhl et al., 1980; Engel et al., 1982; Lee et al., 1994), and over 70% of patients with partial epilepsy show a localised area of decreased cerebral glucose metabolism on ^{18}F-FDG PET. This is usually regional or lobar (Sadzot, 2004); in widespread or multilobar cases, the most hypometabolic lobe is usually the lobe of seizure onset (Sadzot et al., 1992). False localizations have occasionally been

reported in extratemporal epilepsies, but false lateralization is exceptional (Sadzot et al., 1992; Sperling et al., 1995). The sensitivity of ^{18}F-FDG PET is influenced by the location of the seizure focus. In general terms, the sensitivity is greater in temporal than extratemporal epilepsies; Spencer *et al.* reported a sensitivity of 84% in TLE compared to only 33% in extratemporal epilepsy (Spencer, 1994). More recently, in a study specifically addressing ^{18}F-FDG PET findings in FLE, hypometabolic lesions were identified in 55% of patients (Kim et al., 2002).

While PET abnormalities are frequently identified in individuals with a structural lesion on MRI, unfortunately sensitivity is considerably lower in individuals with normal MRI (Ryvlin et al., 1991). In frontal lobe epilepsy, the sensitivity of ^{18}F-FDG PET has been quoted as 73% in individuals with structural lesions on MRI and only 36% of those with a normal MRI (Kim et al., 2002). Despite this lower yield, in clinical practice ^{18}F-FDG PET is most likely to provide useful diagnostic information in the patients in whom the MRI is normal or non-specific; a definitive MRI lesion, when present, is almost invariably more informative than PET data. In general, the use of ^{18}F-FDG PET is limited to localization of the epileptic focus, and there is little capacity to distinguish between different pathologies. However, in neuronal migration disorders, displacement of grey matter activity to a white matter region may occasionally be observed (Lee et al., 1994). This pattern is seen infrequently but when present is highly specific (Sadzot, 2004).

Other PET ligands have been used in epilepsy patients to examine the distribution of various receptors in the interictal state. Most widely used is ^{11}C-flumazenil (^{11}C-FMZ), a selective antagonist of $GABA_A$ receptors (Savic et al., 1988). Evidence is accumulating that ^{11}C-FMZ may be a useful technique for the identification of epileptogenic abnormalities, including patients with extratemporal epilepsies and normal MRI (Richardson et al., 1998; Juhasz et al., 2001; Hammers et al., 2002). Other ligands, including ^{11}C-diprenorphine for opioid receptors and ^{18}F-FCWAY and ^{18}F-MPPF for serotonergic $5HT_{1A}$ receptors, have been used in epilepsy research studies, but their usefulness in FLE has not been examined to date.

Single Photon Emission Computed Tomography (SPECT). SPECT studies involve the administration of blood flow tracers during a seizure. A number of tracers exist for this purpose, including ^{99m}Tc-HMPAO and ^{99m}Tc-ECD. These compounds are lipophilic, and therefore cross the blood-brain barrier; they are then metabolised to hydrophilic compounds that become trapped within cells. Cerebral uptake is complete within 2 minutes of injection, and images of relative blood flow during the seizure can be obtained for up to 3 hours after the administration of the tracer. The sensitivity of ictal SPECT for seizure localization is very high in temporal lobe epilepsy (95%), and is also high in extratemporal epilepsies (90%); the sensitivity of the test falls significantly if the injection is given postictally (Newton et al., 1992). The usefulness of ictal SPECT has been established specifically in FLE, in which it has a sensitivity of 91% (Harvey et al., 1993). However, while SPECT can be effective at localizing seizure onset, it does not provide information on the pathological substrate of the seizure.

9.1d. Pathology and neuroimaging in NFLE

Although seizures in NFLE occur exclusively or almost exclusively during sleep, their semiological features are indistinguishable from those of frontal lobe epilepsy in general. However, the underlying pathological processes involved may be distinct. Personal antecedents such as birth anoxia, febrile convulsions and head injury are less common in NFLE, being reported in 13% of subjects; likewise, abnormalities were seen on cranial imaging with CT or MRI in only 14% (Provini et al., 1999). These findings are unlike those in most partial epilepsies, and are much lower than the 45-60% found in frontal lobe epilepsy as a whole (Swartz, 1989; Cascino, 1992; Mosewich, 2000). Moreover, Autosomal Dominant Nocturnal Frontal Lobe Epilepsy (ADNFLE) comprises up to 25% of cases of NFLE. Taken together, these findings suggest that a 'functional' (as opposed to a 'structural') mechanism may be responsible in many, although not all, cases of NFLE (Provini et al., 1999). In the small group of patients in whom pathological lesions are identified on MRI, the lesions are broadly consistent with the findings of other FLE series, with arteriovenous malformations, cerebral

ischaemic lesions, focal cortical dysplasia and frontal gliosis being reported (Provini et al., 1999).

In terms of functional imaging, there are no specific reports of PET finding in NFLE, other than in two patients with ADNFLE (see later). Ictal SPECT has been reported in two cases of sporadic NFLE, both of which demonstrated anterior cingulate hyperperfusion (Schindler et al., 2001; Vetrugno et al., 2005).

Section 9.2: Autosomal Dominant Nocturnal Frontal Lobe Epilepsy

9.2a. ADNFLE - background

Autosomal Dominant Nocturnal Frontal Lobe Epilepsy (ADNFLE) was first described in 1994 in families from Australia, Canada and the United Kingdom (Scheffer et al., 1994), but has since been described in ethnically diverse populations from around the world, including Italy, Japan, Korea and Norway (Oldani et al., 1998; Nakken et al., 1999; Ito et al., 2000; Cho et al., 2003). When a mutation was discovered in the nicotinic acetylcholine receptor α4 subunit gene in one of these families (Steinlein et al., 1995), ADNFLE became the first human epilepsy in which the fundamental genetic defect had been identified. Subsequently, further mutations in nicotinic acetylcholine receptor α4 and β2 subunit genes have been identified in families around the world (Hirose et al., 1999; De Fusco et al., 2000; Ito et al., 2000; Phillips et al., 2001). These discoveries, along with ion channel mutations in other familial epilepsy syndromes, have led to major changes in the understanding of epilepsy. In particular they led to the concept of epilepsies, including partial epilepsies, as channelopathies.

9.2b. ADNFLE - clinical features

The clinical features of FLE and NFLE have been considered in detail already in Chapters 7 and 8. However, ADNFLE has been studied in some detail as an

independent entity. Seizures usually begin in childhood, with a mean age of onset of around 11 years (Scheffer et al., 1995; Oldani et al., 1998). Although about 85% of cases begin before age 20 (Scheffer et al., 1995), seizure onset has been reported from 1 to 52 years of age (Scheffer et al., 1995; Oldani et al., 1998). In the great majority of cases, affected individuals are of normal intellect and have a normal neurological examination (Scheffer et al., 1995; Oldani et al., 1998), although two familes with mental retardation in association with ADNFLE have been described. In one of these families, mental retardation and ADNFLE were inherited in a bilineal fashion, raising the possibility that the connection was coincidental (Khatami et al., 1998). In the other, however, coexisting ADNFLE and mental retardation were reported in association with the CHRNA4 Ser252Leu mutation in a Korean kindred (Cho et al., 2003). Such a pattern is not found in other reported kindreds, although interestingly some affected members of an unrelated Japanese family with ADNFLE and the CHRNA4 Ser252Leu mutation were reported to have mental retardation (Hirose et al., 1999).

Seizures in ADNFLE occur almost exclusively from sleep, although up to one third of patients may have infrequent daytime seizures, particularly in periods of poor seizure control (Scheffer et al., 1995; Oldani et al., 1998); about one half of subjects may also have rare secondarily generalized tonic-clonic seizures. The majority of patients experience seizures just as they are dozing off to sleep, but seizures may also occur soon before wakening or, less commonly, throughout the night (Scheffer et al., 1995). Patients are often woken by a relatively non-specific aura, often a shiver or feeling in the limbs ; such an aura is more common in ADNFLE (Scheffer et al., 1995) than sporadic NFLE (Provini et al., 1999). The seizure often begins with vocalization, which may be a grunt, moan, or a single word (Scheffer et al., 1995). Prominent motor features are usually seen, including tonic or dystonic posturing, sometimes with superimposed clonic jerking; sitting up or jumping up; bipedal and bimanual automatisms; and sometimes violent behaviour (Scheffer et al., 1995; Oldani et al., 1998). Consciousness is often preserved, and individuals usually experience fear or panic during the seizure; some individuals have prominent vocalization during this period (Oldani et al., 1998). The seizures are typically stereotyped and brief, often one minute or less in duration, and occur in clusters. During clusters, patients usually have six or seven

attacks per night, but in some cases between 20 and 70 attacks per night have been recorded (Scheffer et al., 1995).

Within families there is wide variation in the severity of the disorder (Oldani et al., 1998) and within the manifestations of the seizures themselves (Hayman et al., 1997). In individual subjects, the disorder tends to be at its most severe in childhood and adolescence. Seizures usually become milder and less frequent in adulthood, although rarely completely disappear (Scheffer et al., 1995; Oldani et al., 1998). They are usually responsive to treatment with antiepileptic drugs, with carbamazepine being particularly effective (Scheffer et al., 1995; Oldani et al., 1998; Thomas et al., 1998; Picard et al., 1999; Gambardella et al., 2000); acetazolamide has also been reported as effective in resistant cases (Varadkar et al., 2003). In a single patient with a known α4 nicotinic acetylcholine receptor subunit, nicotine (administered via patch) was found to result in a significant reduction in seizure frequency (Willoughby et al., 2003); however, nicotine has not been used in larger trials in ADNFLE.

9.2c. EEG and neuroimaging in ADNFLE

Interictal awake EEG is usually normal inADNFLE; during sleep, interictal epileptiform abnormalities may be seen in up to 50% of cases, but even when present these are often sparse (Scheffer et al., 1995; Oldani et al., 1998; Picard et al., 2000). Non-specific abnormalities such as frontal theta and delta slowing may be seen in some patients.

Seizures arise from NREM sleep, usually stage 2 but less frequently also from stage 3 or 4. The ictal EEG is often obscured by muscle and motion artifact. When ictal electrographic patterns are discernable they are usually poorly localized, although typically have a frontal predominance. Ictal patterns may comprise rhythmic sharp waves or repetitive 8-11Hz spikes; recruiting rhythms are rarely seen. More often, however, diffuse flattening or rhythmic frontal theta or delta rhythms are recorded (Scheffer et al., 1995; Hayman et al., 1997; Oldani et al., 1998; Provini et al., 1999). In about 25% of cases, both interictal and ictal EEG will be normal (Oldani et al., 1998).

MRI studies are normal in ADNFLE (Scheffer et al., 1995; Oldani et al., 1998; Picard et al., 2000). Interictal PET studies in two unrelated patients showed hypometabolism in the left fronto-polar region in one and the right mid-frontal parasaggital region in the other; in both subjects these regions were hyperperfused on ictal SPECT (Hayman et al., 1997).

9.2d. Clinical Genetics

ADNFLE is inherited in Mendelian autosomal dominant fashion with incomplete (70-80%) penetrance (Steinlein et al., 1995; Steinlein et al., 1997; Oldani et al., 1998; Hirose et al., 1999; De Fusco et al., 2000; Picard et al., 2000). In those families published in the literature, penetrance is quoted from 100% to as low as 29% (Leniger et al., 2003).

However, the family history may be elusive; even once NFLE has been diagnosed in an individual, ADNFLE may only be recognized if a very careful family history is taken. As there is marked variability in severity within families, other family members may have had milder sleep-related events for which they did not seek medical attention; even in more severe cases, the unusual nature of the seizures may have resulted in misdiagnoses (often as parasomnias or pseudoseizures) in family members (Scheffer et al., 1994). A further complication is the increased rates of benign arousal parasomnias (such as sleep terrors, sleepwalking and confusional arousals) reported in ADNFLE families by some authors (Oldani et al., 1996; Provini et al., 1999). It is important both from the perspective of patient management and for molecular genetic studies that such conditions are distinguished accurately.

9.2e. Molecular Genetics – the α4β2 nAChR

Linkage analysis has led to the identification of two definite genetic loci for ADNFLE, which map to chromosome 20q13.2 (ADNFLE Type 1, OMIM #600513), and 1p21 (ADNFLE Type 3, OMIM #605375). Underlying genetic mutations have been identified for both of these loci, all of which are in genes coding for subunits of the neuronal nicotinic α4β2 acetylcholine receptor. There

are, however, many families with unknown linkage; a possible third locus has been identified at 15q24 (ADNFLE Type 2, OMIM #603204), but no associated mutation has been identified here.

In ADNFLE Type 1, four mutations have been identified in the gene coding for the neuronal nicotinic acetylcholine receptor α4 subunit (CHRNA4): three missense mutations, Ser248Phe, Ser252Leu, and Thr265Ile (Steinlein et al., 1995; Hirose et al., 1999; Leniger et al., 2003); and one insertion, 776ins3 (Steinlein et al., 1997). In ADNFLE Type 3, two missense mutations (Val287Leu and Val287Met) have been identified in CHRNB2, the gene coding for the neuronal nicotinic acetylcholine receptor β2 subunit (De Fusco et al., 2000; Phillips et al., 2001). Recently, an additional CHRNB2 mutation (Ile312Met) has been described, occurring de novo in a twin pair with ADNFLE (Bertrand et al., 2005). These recognized mutations in ADNFLE have been identified in families from a variety of ethnic backgrounds, including European, Middle Eastern, Japanese and Korean (Steinlein et al., 1995; Ito et al., 2000; Phillips et al., 2000; Cho et al., 2003).

These findings have led to the concept of ADNFLE as a disorder of the neuronal nicotinic α4β2 acetylcholine receptor (nAChR). The nAChRs are important ligand-gated ion channels which are distributed widely throughout the central nervous system, although the function of these receptors is not fully understood. There is good evidence that they are involved in presynaptic modulation of neurotransmitter release in a number of systems, enhancing the release of norepinephrine, dopamine, GABA, serotonin and acetylcholine (Role and Berg, 1996). In addition there may be direct nicotinic synaptic neurotransmission in the CNS (although there is relatively little evidence of this), and the nAChR is believed to play a role in the regulation of gene expression and neuronal pathfinding during development(Role and Berg, 1996). Functional nAChRs are heteropentameric structures, comprising various combinations of α and β subunits, with the α4β2 subtype (two α subunits and three β) being the predominant form expressed in the human brain. Each nAChR subunit consists of an N-terminal extracellular domain involved in ligand binding, four hydrophobic transmembrane domains and a cytoplasmic loop between domains 3 and 4. The second

transmembrane domain, M2, forms the ion channel pore which appears to be critical; all identified mutations in ADNFLE except one (Leniger et al., 2003) are located in this region.

The clinical features of ADNFLE in families with different mutations appear to be indistinguishable; a direct comparison of families with the CHRNA4 Ser248Phe and CHRNB2 Val287Met mutations did not identify any clinical differences between them (McLellan et al., 2003). One exception to this phenomenon, however, appears to be a possible association between the ser252leu mutation, which has been reported in three families, and increased rates of mental retardation and unresponsiveness to antiepileptic medication (Hirose et al., 1999; Phillips et al., 2000; Cho et al., 2003). Furthermore, the newly identified CHRNB2 Ile312Met mutation appears to be associated with distinct memory deficits; however, this mutation has only been identified in two individuals to date and larger pedigrees await identification to confirm a causal relationship (Bertrand et al., 2005).

ADNFLE, therefore, displays both phenotypic and genetic heterogeneity. The term 'phenotypic heterogeneity' refers to the phenomenon of a single genetic mutation producing a phenotype of widely differing severity; this variability may be seen within a given family (Scheffer et al., 1995). Genetic heterogeneity, on the other hand describes different mutations causing a similar phenotype, and takes two forms; allelic heterogeneity, referring to different mutations at the same locus, and locus heterogeneity, referring to mutations at different loci. Both forms of genetic heterogeneity are seen in ADNFLE. In fact, the situation may be even more complex: the fact that the known nAChR mutations have not been identified in so many of the established cases of ADNFLE raises the possibility of an alternative mechanism, unrelated to the nAChR genes, in some individuals (Combi et al., 2004).

9.2f. Functional consequences of α4β2 nAChR mutations in ADNFLE

Although seven mutations in α4β2 nAChR subunit genes have been identified to date, the mechanism by which these cause ADNFLE is not entirely clear. A number of *in vitro* studies have been performed in an attempt to clarify the functional consequences of the recognised mutations on receptor function and help explain the pathogenesis of this condition. Most such studies have expressed mutant α4β2 receptors in *Xenopus* oocytes and compared various physiological parameters of these receptors with non-mutant receptors. Early studies demonstrated a number of physiological effects of the receptor mutations, including increased receptor desensitization, reduced mean ACh-evoked current amplitude, and reduced calcium permeability (Kuryatov et al., 1997; Steinlein et al., 1997; Bertrand et al., 1998). As these properties implied a loss of nAChR function, it was initially hypothesised that ADNFLE results from a reduced modulatory effect of ACh on other neurotransmitter systems (Weiland et al., 2000).

However, these initial studies were criticised on the grounds that the receptor populations examined in the experiments differed from those in ADNFLE patients in two important respects: firstly, the cDNA used was obtained by genetic engineering and may therefore have been different in some way to that seen in patients; and secondly, the *Xenopus* oocytes studied contained only mutant receptor subunits. As ADNFLE is an autosomal dominant condition, and patients are heterozygotes for the CHRNA4 or CHRNB2 genes, both normal and mutant subunits should be expressed in the *Xenopus* oocytes being studied (Bertrand et al., 2002). When heterozygous receptors were generated and studied in subsequent experiments, the properties observed were quite different to those seen in the homozygous forms. Bertrand et al. studied four ADNFLE mutations (α4Ser248Phe, α4776ins3, α4Ser252Leu, and β2 Val287Leu) expressed in a heterozygous fashion. Interestingly, many of the abnormalities seen in the homozygous condition disappeared; features such as receptor desensitisation and ACh-evoked current amplitude were indistinguishable in mutant and control receptors. All four mutations produced one common trait, however, which was an

increase in receptor ACh sensitivity. This finding was important for two reasons: firstly it provided a common mechanism for all mutations involved in ADNFLE, which would be expected from the clinically indistinguishable phenotypes produced by the different mutations; and secondly, it led to a new hypothesis in which ADNFLE is produced by a gain of α4β2 nAChR function, rather than a loss of function as previously believed (Bertrand et al., 2002).

This hypothesis was supported by further work (on the same mutations plus the β2Val287Met mutation) which demonstrated reduced Ca^{2+} - induced increases in the ACh response in all five ADNFLE mutations; in other words, the mutations reduced the Ca^{2+} dependence of α4β2 nAChR activity (Rodrigues-Pinguet et al., 2003). As Ca^{2+} dependence may prevent presynaptic α4β2 nAChR from overstimulating glutamate release at excitatory synapses, the authors suggested that the reduction in the Ca^{2+} sensitivity (producing a gain of α4β2 nAChR function) may result in increased α4β2 – stimulated glutamate release and hence to seizures.

Finally, circumstantial evidence for a gain of α4β2 nAChR function in ADNFLE comes from the clinical and experimental responses to carbamazepine. Carbamazepine has been reported as one of the most effective antiepileptic drugs in the treatment of ADNFLE in clinical practice (Scheffer et al., 1995). Moreover, it has been found to act as a non-competitive inhibitor at the α4β2 nAChR, with the α4Ser248Phe and α4776ins3 mutant receptors showing a greater sensitivity to this inhibitory effect (Picard et al., 1999). Interestingly, in the hetrozygous receptors studied by Bertrand et al, it was found that all mutations showed increased sensitivity to blockade by carbamazepine compared to controls except for the α4Ser252Leu; this is the mutation which has clinically been associated with a clinical ADNFLE phenotype that is more resistant to pharmacotherapy and a poor response to carbamazepine (Hirose et al., 1999; Cho et al., 2003). These findings would support a gain of function of the α4β2 nAChR resulting in theADNFLE phenotype.

Interestingly, a possible link between this proposed gain of function and the nocturnal seizures of NFLE has been proposed on the basis of an [^{18}F] –F-A-

85380 PET study. Binding of [^{18}F] –F-A-85380, a high affinity α4β2 nAChR agonist, was examined in 8 subjects with ADNFLE and a confirmed mutation in either *CHRNA4* or *CHRNB2*. Compared to a normal comparison group, the ADNFLE group demonstrated *increased* [^{18}F] –F-A-85380 binding in the mesencephalon, cerebellum and pons, with *reduced* binding in the right prefrontal cortex. The authors hypothesise that the increased receptor density observed in brainstem and mesencephalic structures observed may result in hyperfunction of cholinergic pathways involved in sleep and arousal. As a result, *physiological* thalamocortical oscillations in sleep such as spindles (which, like the seizures of ADNFLE, are common in stage 2 NREM sleep) may develop into *pathological* thalmocortical oscillations, resulting in seizures (Picard et al., 2006). Although at present this hypothesis is based on a small patient sample, it is interesting and warrants further consideration.

9.2g. Molecular genetics – possible non-α4β2 mechanisms

Despite the considerable evidence for involvement of the α4β2 nAChR in ADNFLE, only a minority of patients with the condition carry one of the identified mutations. Screening studies in sporadic NFLE and ADNFLE patients have had a very low pick up rate for these mutations (Tenchini et al., 1999; Duga et al., 2002; Combi et al., 2004); from the available literature it has been estimated that they account for less than 10% of all cases of ADNFLE (Combi et al., 2004). Recently, two studies have suggested that alternative molecular mechanisms, unrelated to α4β2 dysfunction, may be responsible for ADNFLE in some families.

Combi *et al.* reported two polymorphisms in the promoter region of the corticotrophin releasing hormone (CRH). One of these was found to cosegregate with ADNFLE in three familes, but is a recognised polymorphism occurring in approximately 3% of normal controls. The other was not found in any controls, suggesting that it is a mutation, but was found in only a single subject with ADNFLE. *In vitro* studies demonstrated that both these polymorphisms had functional consequences, with the former causing an increase in CRH expression but the latter producing a decrease (Combi et al., 2005). Thus while overall these findings suggest a possible role for the CRH gene in ADNFLE, they fall short of

providing conclusive evidence; further work is needed to clarify the nature of any association.

More recently, however, more convincing evidence for involvement of the α2 nAChR subunit was presented. Aridon et al. described a large family with ADNFLE in whom a homozygous missense mutation, I279N, was identified in the neuronal nicotinic acetylcholine α2 subunit gene (*CHRNA2*). This mutation localizes to the first transmembrane domain (M1) of the α2 nAChR subunit, which is not a direct component the receptor's ion-gating structure, but may alter the relative movements of other parts of the receptor during the gating process. Functional studies indicated that the *CHRNA2* mutation results in a marked increase in receptor sensitivity to acetylcholine (Aridon, 2006).

9.2h. Familial Partial Epilepsy with Variable Foci (FPEVF)

Finally, a further genetic syndrome often associated with NFLE should be considered at this point. Familial Partial Epilepsy with Variable Foci (FPEVF) frequently presents with nocturnal seizures of suspected or proven frontal lobe origin (Scheffer et al., 1998; Berkovic et al., 2004); the condition may be confused with ADNFLE, as the family history reveals other affected individuals with epilepsy inherited in an autosomal dominant fashion. However, in contrast to ADNFLE, in FPEVF not all affected family members have nocturnal tonic or hyperkinetic frontal lobe seizures. Seizure patterns and EEG localisation indicating frontal, temporal centroparietal and occipital lobe epilepsy have all been recognised in family members in FPEVF, although affected individuals have a constant seizure type throughout their lives (Scheffer et al., 1998). In those individuals with an NFLE phenotype, the clinical pattern in FPEVF is often somewhat different to that seen in ADNFLE. In FPEVF, frontal lobe seizures occur both from wakefulness and sleep, secondarily generalise more frequently, and often occur singly in a night rather than in the clusters seen in ADNFLE (Berkovic et al., 2004).

To date, several families with this condition have been described (Scheffer et al., 1998; Xiong et al., 1999; Picard et al., 2000; Callenbach et al., 2003). As with

other idiopathic focal epilepsies, all affected members have normal cerebral imaging on MRI. One Australian family was reported to have prominent interictal epileptiform discharges on EEG (Scheffer et al., 1998); in other families, interictal discharges are seen only infrequently (Xiong et al., 1999; Callenbach et al., 2003).

Linkage studies in the Australian family suggested localisation of the gene to chromosome 2q, wheras there has been strong evidence from other families from Spain, Canada and the Netherlands of linkage to Chromosome 22q12. It seems likely that at least two clinical forms of FPEVF exist with different genetic substrates, although the number of case reports in the literature to date is relatively low.

Conclusions.

Frontal lobe epilepsy has a wide range of pathological correlates. Gliosis secondary to trauma or infection, cortical dysplasia and tumours are all seen commonly, with corresponding features on neuroimaging. Interestingly, however, in both sporadic and familial NFLE, pathological lesions are found in only a small number of cases. This finding suggests that other mechanisms may be important in NFLE, a fact borne out by the recognition of the syndromes of ADNFLE and FPEVF which are clearly genetic in origin. The identification of mutations in genes coding for subunits of the $\alpha 4\beta 2$ nAChR in ADNFLE has led to significant changes in the understanding of epilepsies and introduced the concept of epilepsies as channelopathies.

CHAPTER 10

FRONTAL LOBE EPILEPSY
Aspects of differential diagnosis

Introduction

The diagnosis of frontal lobe epilepsy (FLE) can be difficult. The wide range and often bizarre nature of presenting features, combined with frequently normal or non-specific interictal and ictal EEG findings, can easily result in misdiagnosis. During wakefulness, the most troublesome distinction is with psychogenic non-epileptic seizures (PNES), also known as pseudoseizures. It is now increasingly recognized that some individuals previously diagnosed with non-epileptic events in fact have frontal lobe seizures. The situation is even more problematic when frontal lobe seizures are restricted to sleep; many non-epileptic sleep disorders are also characterized by paroxysmal motor activity, and differentiating these conditions from NFLE may not be straightforward (Scheffer et al., 1994; Zucconi and Ferini-Strambi, 2000). In general, the most common source of diagnostic confusion is with the NREM arousal parasomnias such as sleep terrors and somnambulism. However, the spectrum of motor disorders of sleep is wide, and a diagnostic uncertainty may arise in a number of situations depending on the referral base of the clinician involved.

This chapter is divided into three sections. Section 1 is a discussion of PNES, the main differential diagnosis of FLE during wakefulness; Section 2 comprises a review of non-epileptic motor sleep disorders, as classified by the International Classification of Sleep Disorders (ASDA, 2000); and in Section 3 the important clinical features enabling discrimination between NFLE and other sleep disorders, particularly the NREM parasomnias, are considered.

Section 10.1. Differential Diagnosis Of Frontal Lobe Seizures In Wakefulness: PNES

The most important differential diagnosis of diurnal frontal lobe seizures is psychogenic non-epileptic seizures (PNES). These have been recognized for centuries and were well studied by Charcot and Gowers in the 19th century (Charcot, 1877; Gowers, 1964). However, since the spectrum of behaviours associated with FLE has been more widely recognized, it has become apparent that these conditions are easily confused, particularly by clinicians with limited direct experience of FLE (Williamson, 1995). This issue has significant practical implications. Failure to recognize epilepsy will result in patients being denied appropriate investigation and management; if, on the other hand, PNES are not recognized (particularly in prolonged events mimicking status epilepticus) the patient may be subjected to inappropriate, expensive, and potentially harmful treatment (Wilner and Bream, 1993; Tuxhorn and Fischbach, 2002).

10.1a. Definition and pathology of PNES

Psychogenic non-epileptic seizures (PNES) are defined as psycogenically determined clinical events that resemble epileptic attacks but are not associated with neurophysiological dysfunction (Ozkara, 1993; Andriola and Ettinger, 1999). A small minority of these cases are factitious in origin, with conscious fabrication of symptoms to maintain a sick role (as in Munchausen's syndrome) or to obtain some other recognizable benefit (Krumholz, 1999). However, in the great majority cases, PNES are considered to be a somatoform disorder, thus requiring a psychiatric approach to treatment (Krumholz, 1999).

A detailed discussion of the psychopathology of PNES and somatoform disorders is beyond the scope of this review, but the condition is heterogeneous in origin. A number of mechanisms appear to be involved, including dissociation reactions to abuse or trauma (Bowman, 1996; Devinsky, 1996; Akyuz et al., 2004), underlying personality disorders (Vanderzant, 1986; Bowman, 1996) and posttraumatic stress

disorder (Bowman, 1996). In addition, other psychiatric co-morbidities such as depression and anxiety are common in patients with PNES (Bowman, 1999).

10.1b. Clinical Features of PNES – the history.

PNES may present in a variety of ways, with generalized convulsive features, altered consciousness or focal features. Gulick et al (1982) divided PNES into four major groups based on the predominant clinical phenomena: those characterized by bilateral motor activity; those with unilateral motor activity; those showing multiple phenomena; and those characterized by decreased responsiveness alone. As a result, they can superficially resemble any of the major seizure types including generalized tonic clonic seizures, complex partial seizures of temporal and frontal lobe origin, and absence seizures (Gulick, 1982; Boon and Williamson, 1993). While it is often very difficult to make a definitive diagnosis of PNES from the clinical history alone, some features may raise the suspicion of this diagnosis. These include a long-standing history of non-stereotyped attacks unresponsive to anticonvulsant medications (Boon and Williamson, 1993), prolonged duration of episodes (Krumholz, 1999), precipitation by emotional situations (Trimble, 1986), and unusual behaviours such as ictal weeping (Walczak, 1996). The social history may be as important as the medical data in these individuals (Boon and Williamson, 1993).

10.1c. Clinical features of PNES - Video EEG monitoring

Often video EEG monitoring (VEM) is the only way to accurately characterize PNES. If events are occurring frequently enough, this may be possible in the outpatient setting (Watemberg et al., 2005). PNES can often be provoked by emotional stimuli or suggestion (Cohen, 1982; Walczak, 1994; Zalsman et al., 2002), a feature recognized by Charcot in the nineteenth century (Massey, 1986), and some authors advocate the routine provocation of PNES for diagnostic purposes. For example, administration of intravenous saline, while suggesting this will induce a seizure, may be sufficient to precipitate an event (Slater et al., 1995). Although such techniques generally involve misleading the patient, making their

use in routine clinical practice ethically questionable, some authors have argued that it is possible to undertake such testing honestly and ethically (Devinsky, 1996).

More commonly, however, admission for formal video EEG monitoring is required. The reported PNES events recorded on video-EEG monitoring fall into to major categories: convulsive events, broadly resembling generalized tonic-clonic seizures; and events broadly resembling complex partial seizures.

PNES resembling generalized tonic-clonic seizures. The most widely studied group of PNES is characterized by generalized convulsive movements (Gulick, 1982; Gates, 1985). However, the nature of these events is almost invariably different to generalized tonic clonic seizures (GTCS), and they will not usually be confused by an experienced observer.

True GTCS follow a characteristic and well-described pattern (Rodin, 1981) with loss of consciousness, brief flexion of the upper limbs and often a cry, followed by jaw clenching and cessation of respiration associated with tonic limb extension in which the upper limbs are usually kept alongside the body. This tonic phase is followed after about 35 seconds by clonic 'in phase' jerking of the limbs, usually symmetrical in nature, which also usually lasts around 35 seconds and ends with a deep inspiration and subsequent stertorous breathing. Post-ictally there is initially stupor, followed by confusion within minutes. Often the patient will then fall asleep. These seizures may be associated with tongue biting (usually on the lateral aspect) and excessive salivation, and urinary (although very rarely bowel) incontinence may occur.

In contrast, PNES usually comprise thrashing, trembling, writhing, 'out of phase' limb movements and pelvic thrusting; these features are very rare in GTCS (Gulick, 1982; Gates, 1985; Leiss, 1992). Movements often also appear to have a semipurposeful quality, and consciousness is often retained (Krumholz, 1999). The characteristic GTCS sequence is not seen; events often have a 'waxing and waning' quality, with recurrent periods of motor activity interspersed with quiet

unresponsiveness (Gulick et al, 1982). They generally last significantly longer than GTCS (Gates, 1985) and post ictal recovery is often rapid (Krumholz, 1999).

PNES resembling complex partial seizures. Although the distinction with GTCS is usually relatively straightforward if events are recorded on VEM, it can be more difficult to distinguish these behaviours from complex partial seizures, particularly those of frontal lobe origin. Many of the bizarre features of frontal lobe complex partial seizures, discussed in Chapter **7**, are also seen in pseudoseizures. Features common to both conditions include pelvic thrusting, retained awareness, vocalization and sexual automatisms (Saygi, 1991; Geyer et al., 2000). Typically, neither type is associated with significant post-ictal confusion (Saygi, 1991), and although frontal lobe seizures are usually more stereotyped in nature, PNES may be highly stereotyped within subjects too (Gulick et al. 1982). Forced eye closure, trembling, slow evolution, a waxing and waning quality and prolonged duration are also more suggestive of PNES than frontal lobe epilepsy (Andriola and Ettinger, 1999; Krumholz, 1999). In a direct comparison of frontal lobe epilepsy and NPES, Saygi et al. found that younger age of seizure onset, the presence of MRI abnormalities, short ictal duration, seizures with a prone posture and nocturnal occurrence were useful indicators of FLE rather than PNES.

It should be noted that a significant number of PNES are characterized by reduced responsiveness with few or absent motor features; in some reported series this is the most common event type (Leiss, 1992). The majority of such events are associated with a non-specific 'aura' (Gulick, 1982; Leiss, 1992), which is usually followed by unresponsiveness. Such events can be very difficult to distinguish from temporal lobe epilepsy (or occasionally absence seizures) on the grounds of seizure semiology.

EEG findings. In events characterised by prominent motor manifestations, the EEG will be normal or be obscured by muscle or movement artifact (Krumholz, 1999). This is not necessarily useful in distinguishing episodes from frontal lobe seizures, which may also be associated with normal or non-specific EEG changes in up to 50% of cases (Zucconi and Ferini-Strambi, 2000). Likewise, if the patient is reporting subjective sensations without observed behavioural change, a normal

EEG is also unhelpful as simple partial epileptic seizures (with retained awareness) may be associated with normal scalp EEG (Devinsky, 1988). However, in the presence of clinically altered awareness, preservation of normal awake background rhythms is not consistent with epileptic events and is typical of PNES (Leiss, 1992). Testing of awareness during events is therefore important in this setting.

10.1d. Epidemiology

PNES are common. They are reported to account for 5 to 20% of patients with intractable epilepsy (Desai, 1979; King, 1982), and 10 to 40% of admissions for video EEG monitoring (Meierkord et al., 1991; Krumholz, 1999). They may occur in any age group, from childhood to old age, although most commonly present between the ages of 15 and 35 years (Krumholz, 1983). As with other somatoform disorders they occur more commonly in females, with women constituting 70 to 80% of cases in most reports (Meierkord et al., 1991; Walzack, 1995).

10.1e. Psychological and psychiatric considerations

In addition to psychopathology *per se*, a number of predisposing factors for PNES have been described. The most widely reported is a history of sexual abuse, with studies reporting such a history in between 25 and 67% of patients with PNES (Alper, 1993; Bowman, 1996). Physical abuse and other trauma is also widely reported (Harden, 1997; Fleisher et al., 2002), and head trauma, often mild, may precipitate these events in some individuals (Barry, 1998). In addition, a co-occurrence of PNES has been widely reported in both children and adults with epilepsy (Ramani, 1980). The exact incidence is unclear, with between 10% and 40% of individuals with PNES also having established epilepsy (Lesser, 1996; Krumholz, 1999). Often in this situation, the epileptic seizures are well controlled and the PNES are the troublesome events (Devinsky, 1996). PNES may provide such individuals with means of gaining attention or maintaining the sick role, or may arise in the presence of a concomitant personality disorder or impaired coping mechanisms (Krumholz, 1999).

Some authors have reported a 'typical' patient profile with PNES. This is a female, usually with low intelligence and a personality disorder, and often with other psychiatric diagnoses including depression, anxiety and suicide attempts (Boon and Williamson, 1993). While some of these observations may be valid, some individuals with epilepsy may also exhibit many of these traits. Several authors have cautioned against using psychological profiles to distinguish between NPES and epilepsy, while bearing in mind that psychiatric assessment can provide important diagnostic information (Boon and Williamson, 1993)

10.1f. Prognosis

The outcome of PNES is dependent upon a number of factors. In general, children and adolescents have a better outcome than adults; one major study reported approximately 50% seizure freedom immediately after diagnosis and almost 80% at two years (Wyllie, 1991). Studies in adult populations indicate 20 to 50% of patients are seizure free at 1 year, with a similar figure at 5 years (Krumholz, 1983; Bowman, 1999). Clinical features including personality disorder, recurrent major depression, and denial of stressors and psychosocial problems have been associated with a poor prognosis (Kanner et al., 1999), as have a prolonged duration of PNES, persistent somatization, and unfavourable family dynamics (Bowman, 1999). The diversity of underlying psychiatric disorders presenting with pseudoseizures means that tailored treatment approaches are required for individual patients, and as such the value of individual strategies has not been widely assessed. Most authors agree, however, that both psychiatric treatment and supportive neurological input is necessary in the management of PNES (Aboukasm, 1998; Bowman, 1999; Kanner et al., 1999).

Section 10.2. Non-Epileptic Motor Disorders Of Sleep

Non-epileptic motor disorders of sleep are common and take a wide variety of forms. Using the International Classification of Sleep Disorders (ICSD), developed by the American Sleep Association (ASDA, 2005), they can be broadly grouped into parasomnias, sleep related movement disorders, and 'others'. When considering the differential diagnosis of NFLE, it is important to consider the full range of these conditions, which are summarized on Table 1 and discussed in the following section.

10.2.1. Parasomnias

This group of sleep disorders is most frequently confused with NFLE. Parasomnias are defined in the International Classification of Sleep Disorders (ICSD-2) as 'unpleasant or undesirable behavioural or experiential phenomena that occur predominantly or exclusively during the sleep period' (ASDA, 2005). They are subdivided on the basis of the phenomenology into three subgroups: disorders of arousal (from NREM sleep), parasomnias usually associated with REM sleep, and others (Table 1.)

NREM Arousal Disorders.

Definition and clinical features

Arousal disorders characteristically occur during deep non-REM sleep (slow wave sleep) and are attributed to impaired arousal mechanisms. They are the most frequently encountered parasomnias, usually beginning in childhood and resolving in adolescence, and are the most important group from the perspective of diagnostic confusion with epilepsy. The arousal disorders are characterised by paroxysmal motor behaviours without conscious awareness, and have a broad spectrum of clinical manifestations. In clinical practice, they are subdivided into three main forms: *confusional arousals*, which are associated with little motor or autonomic involvement; *somnambulism* (sleepwalking), which is associated with

I. Parasomnias

a. NREM Arousal disorders
   i. Confusional arousals
   ii. Sleepwalking
   iii. Sleep terrors
b. Parasomnias usually associated with REM sleep
   i. REM sleep behaviour disorder
   ii. Parasomnia overlap disorder
   iii. Sleep paralysis
c. Other parasomnias
   i. Catathrenia (nocturnal groaning)

II. Sleep-related movement disorders

a. Periodic limb movements of sleep
b. Sleep bruxism
c. Nocturnal leg cramps
d. Rhythmic movement disorder (jactacio capitis nocturna)

III. Other (non-parasomnia, non-movement disorder) paroxysmal nocturnal events

a. Sleep starts
b. Somniloquy
c. Benign sleep myoclonus of infancy
d. Nocturnal psychogenic non-epileptic seizures (PNES, pseudoseizures)
e. Nocturnal panic attacks
f. Sleep-related breathing disorders
g. Gastroesophageal reflux
h. Newly recognized conditions
   i. Excessive fragmentary myoclonus
   ii. Propriospinal myoclonus at sleep onset
   iii. Rhythmic feet movements while falling asleep
   iv. Alternating leg muscle activation during sleep and arousals

Table 10. 1. *The major Paroxysmal Motor Disorders of Sleep, categorized according to the International Classification of Sleep Disorders (ASDA, 2005.)*

motor activity but little autonomic involvement; and *sleep terrors (pavor nocturnus)*, in which prominent autonomic involvement is observed accompanied by a variable degree of motor activity. Although these groupings are used in practice, based on the predominant clinical features observed, common underlying mechanisms are believed to be responsible. Similar electroclinical features are seen in each group, and affected individuals may display features of more than one subtype.

Confusional arousals are characterized by sudden arousal with disorientation and confusion, sometimes associated with some semipurposeful behaviours. Vocalisation, and sometimes coherent speech, is common, and the patient may appear upset. Some individuals may become aggressive or agitated, particularly if attempts are made to console or waken them. The events may be brief, lasting only one or two minutes, but may continue for ten minutes or more (sometimes considerably longer) during which time the patient is very difficult or impossible to awaken (Aldrich, 1999; Sheldon, 2000).

During *somnambulism,* the most common manifestation of the arousal disorders, affected individuals display simple or complex motor behaviours during sleep, typically associated with getting out of bed and walking. Patients will often walk out of the bedroom, sometimes leaving the home, and may conduct purposeful or semipurposeful tasks such as moving objects, talking (although often nonsensically), dressing, eating and drinking (Aldrich, 1999), and even driving (Schenck and Mahowald, 1995). Some individuals will appear frantic and agitated; sexual and violent behaviours have occasionally been reported (Rosenfeld and Elhajjar, 1998), and sleepwalking has been used successfully as a defence against a charge of murder (Broughton et al., 1994). The episodes may last from a few minutes to over 30 minutes, and usually end with the patient returning to bed and to sleep; some sleepwalkers will respond to a command to return to bed. One widely reported variant of somnambulism (although not yet listed as a specific disorder in the ICSD) is sleep related eating disorder (SRED), in which individuals leave the bed to eat during sleep. It often occurs in individuals with no other history of parasomnias, predominantly affects women

with onset around 25 years of age, and may be triggered by a number of factors including stress, dieting or psychotropic drug use (Schenck et al., 1991).
Sleep terrors are the most dramatic arousal disorders, characterized by prominent autonomic and affective features. The individual will suddenly arouse from deep sleep, usually with a 'blood-curdling' scream, and appear pale and terrified. There is often agitated behaviour and sometimes the individual will attempt to leave the room; extreme agitation may result in injuries from jumping out of windows or down stairs. Autonomic features, including tachycardia and diaphoresis, are prominent. Individuals are usually inconsolable and difficult to wake and the event may last from a matter of minutes to 10 minutes or longer.

Although the arousal disorders are subdivided in this manner, in reality there is considerable overlap between the groups. In general, individuals have no recollection of the events, although some will report vague recollections of terrifying situations (Aldrich, 1999). A number of precipitating factors are recognized, including febrile illness, sleep deprivation or a chaotic sleep schedule, and emotional stress (Sheldon, 2000), although interestingly they appear to decline during pregnancy (Hedman et al., 2002).

Epidemiology

Arousal disorders are common disorders of childhood, occurring in an estimated 15-20% of preadolescent children (Laberge et al., 2000; Agargun et al., 2004). The prevalence of sleep terrors has been estimated at 1% - 6.5% (DiMario and Emery, 1987),with somnambulism affecting up to 15% of individuals at some time during childhood or adolescence (Jacobson, 1969). Sleep terrors tend to begin at around 18 months of age, with a peak prevalence at 5-7 years of age (DiMario and Emery, 1987); confusional arousals also occur in very young children, usually under 5 years of age (Leo, 2003). Sleepwalking usually occurs a little later in childhood (Zaiwalla, 2005). Arousal disorders infrequently persist into adulthood; while the prevalence of sleepwalking is estimated at 15% in childhood, it is only 1% to 4% in adulthood (Cirignotta, 1983; Hublin et al., 1997).

Pathophysiology

The arousal disorders are so named because they are believed to arise through incomplete or impaired arousal from deep NREM sleep (Broughton, 1968); there is therefore a dissociation between the behavioural state, with waking behaviours observed, and the EEG which often shows sleep patterns. A recent SPECT study performed during an episode of somnambulism supported this concept, showing increased cerebral blood flow in some regions (mainly the posterior cingulate cortex and cerebellum), but reduced blood flow consistent with deactivation in large areas of frontal and parietal association cortex (Bassetti et al., 2000). Due to their high prevalence in otherwise normal children they are usually considered to represent altered physiological processes rather than true pathology.

Although analyses of sleep macrostructure show no significant differences between adult somnambulistic patients and controls (Schenck et al., 1998; Gaudreau et al., 2000), there is evidence of microstructural abnormalities and abnormal arousal in individuals with parasomnias. These individuals have fragmented sleep, with more frequent arousal and awakenings from slow wave sleep compared to controls (Espa et al., 2000; Gaudreau et al., 2000). EEG studies with spectral analysis indicate that, while the slow wave power is lower overall during the early periods of deep NREM sleep (Gaudreau et al., 2000) the intensity of slow wave sleep immediately prior to a parasomnia is unusually increased (Espa et al., 2000). Cyclic alternating pattern (CAP) rate, a measure of NREM instability, is also increased in individuals with parasomnias (Zucconi et al., 1995). Arousal disorders are, therefore, conceptualized as an inability to maintain consolidated slow wave sleep (Joncas et al., 2002), possibly due to coexistent disorders causing frequent arousal in slow wave sleep (Espa et al., 2002). This hypothesis is supported by the increasing evidence that adult somnambulism is significantly associated with obstructive sleep apnoea (Pressman et al., 1995; Espa et al., 2002). Treatment with CPAP has been shown to be effective in controlling both sleep apnoea and the parasomnias in these individuals (Guilleminault et al., 2005), and there is also evidence that such mechanisms may be relevant in children (Guilleminault et al., 2003).

While the frequency of arousals is important, however, it is not the only relevant factor in the development of these conditions; individuals with obstructive sleep apnoea, for example, have very frequent arousals but do the majority do not sleepwalk. It is possible that abnormally deep slow wave sleep at the time of the arousal makes full awakening difficult, resulting in a disordered arousal leading to a parasomnia (Espa et al., 2000). This hypothesis is supported by the fact that prior sleep deprivation increases the frequency of somnambulistic episodes in sleepwalkers (Joncas et al., 2002). While this unusual intensity of sleep is not well understood it may, in some cases, result from drug administration. Sleepwalking is associated with a number of drugs which are known to influence NREM sleep, including lithium, zolpidem (alone and in combination with serotonin specific re-uptake inhibitors) and olanzapine (Landry et al., 1999; Kolivakis et al., 2001; Lange, 2005). These drugs appear to increase the intensity of slow wave sleep, and thereby raising the possibility of a disordered arousal and a parasomnia.

The high prevalence of arousal disorders in childhood may result from incomplete maturation of chronobiological mechanisms. These mechanisms, which govern slow wave sleep and arousal, are responsible for normal sleep cycling. Minor changes in routine may result in desynchronisation of normal rhythms in children, resulting in internal arousal stimuli coming at the 'wrong time' causing incomplete arousal from very deep sleep. As development continues, these mechanisms mature, synchronisation occurs and the symptoms resolve unless an alternative pathology such as sleep apnoea exists (Sheldon, 2000). Some authors have proposed that the serotonergic system is the key substrate in this process. Activation of this system is known to be partially responsible for arousal, as well as having a role in motor activity (Jacobs and Fornal, 1999); in addition, the serotonergic system is normally activated by hypercapnia (Richerson et al., 2001). It is proposed that in individuals who sleepwalk there is abnormal excitability of the serotonergic system which, when activated independently of other neurotransmitters involved in arousal, results in motor behaviours but incomplete arousal. It is proposed that hypercapnia during obstructive sleep apnoea triggers this system in susceptible individuals, resulting in a parasomnia (Juszczak and Swiergiel, 2005).

Finally, the mechanisms by which 'awake' behaviour occurs in an 'asleep' brain in these disorders are unclear. Some authors have speculated that the central pattern generators proposed to underpin epileptic automatisms (see Chapter 7, page 136) are also activated in parasomnias (Mahowald, 2002; Tassinari et al., 2005). Ambulation and apparent fear are the main behavioural features of these disorders. The hypothesis that they are subcortically encoded survival patterns, and that they are somehow released from inhibition during sleep during parasomnias, is plausible. However, at present, no detailed semiological or physiological data exists to support or oppose such a premise. If similar mechanisms are responsible for parasomnias and NFLE one would expect very similar, possibly indistinguishable, semiological features, but sufficiently detailed studies of parasomnias have not been reported to assess this.

Psychiatric disturbance and the arousal disorders

Until recently, it was widely assumed that arousal parasomnias, particularly if associated with violence, were the result of significant psychiatric pathology or unresolved psychological stress (Schenck and Mahowald, 2000). This belief can be traced back centuries, with the disturbed wanderings of Lady Macbeth providing the prototypical example; the fact that stress often appears to precipitate these attacks probably strengthened this belief. Some early studies showed increased rates of psychopathology in adults with arousal disorders, apparently supporting this view (Fisher et al., 1974; Kales et al., 1980; Schenck et al., 1989; Llorente et al., 1992). However, the findings of more recent studies have largely refuted this belief, indicating that psychopathology and parasomnias are not associated by their onset, clinical course, or treatment (Schenck et al., 1989; Guilleminault et al., 1995; Moldofsky et al., 1995; Schenck and Mahowald, 2000). Other authors have identified psychological stress as just one of a number of contributory factors in the development of these disorders (Moldofsky et al., 1995).

Parasomnias associated with REM sleep

REM Sleep Behaviour Disorder (RBD)

Clinical features and associated pathology. This disorder is characterized by a loss of atonia during REM sleep resulting in the acting out of dream content (termed oneiric behaviours). The condition was first described by Jouvet in a feline model (Jouvet, 1965). In these studies, REM sleep without atonia and behaviours resembling 'oneirism' were noted following bilateral lesions of pontine regions surrounding the locus coeruleus. REM Sleep Behaviour Disorder (RBD) in humans, however, was not described until 1986 (Schenck, 1986). As in the animal model, impairment or loss of the usual muscle atonia of REM sleep results potential harmful dream-enacting behaviours. During REM sleep, patients will display complex dramatic, agitated and often violent behaviours such as speaking, screaming, punching and kicking, jumping out of bed and running (Schenck and Mahowald, 2002). These may result in injury to the patient or their bedpartner (Olsen, 2002). Patients are not in contact with the environment during these episodes but can usually be wakened, when they will often (but not invariably) report vivid dream mentation (Fantini et al., 2005); they also often report more vivid and intense dreams coincident with the onset of RBD (Schenck and Mahowald, 2002). If left alone, patients will usually return to sleep and remain oblivious to their sleep behaviour. Episodes may last from a few minutes to half an hour, and while some patients will have episodes several times per night, in others they will be much less frequent. Events occur preferentially in the second half of sleep, when the greatest proportion of REM sleep occurs (Schenck, 1986). Clonazepam is usually effective in preventing or controlling the episodes (Schenck and Mahowald, 2002).

RBD may present clinically as either an acute or chronic condition. Acute RBD may be precipitated by certain drugs, particularly tricyclic or SSRI antidepressants (Schenck, 1992), or by the withdrawal of alcohol, benzodiazepines or barbiturates (Silber, 1996); in this situation the condition usually develops abruptly and is usually short-lived. Precipitation by acute psychological stress has also been occasionally reported (Hefez, 1987; Sugita, 1991).

A strong association between chronic RBD and degenerative neurological conditions has been reported, with Parkinson's disease (PD) and Multiple System Atrophy (MSA) by far the most common, although other parkinsonian syndromes, narcolepsy, dementia, cerebrovascular disease, multiple sclerosis and Machado-Joseph disease have also been causally associated in some cases (Schenck, 1993; Sforza et al., 1997; Olsen, 2002; Schenck and Mahowald, 2002; Friedman et al., 2003). Such an association is seen in about 60% of RBD patients (Olsen, 2002) and the sleep disorder may precede the waking manifestations of the underlying condition by several years (Schenck, 1996; Plazzi, 2004). When no neurological lesion or disorder is identified the term 'idiopathic RBD' is used. However, even among this group there is now increasing evidence that RBD is an early manifestation of a more pervasive neurodegenerative process, rather than a simple parasomnia *per se* (Fantini et al., 2005). There are a small number of reports of RBD in children, often in association with brainstem pathology or narcolepsy, but also occasionally without known central nervous system pathology (Sheldon and Jacobsen, 1998).

RBD variants. Some variants of RBD warrant specific mention. *Parasomnia overlap disorder* consists of overlapping NREM and REM motor parasomnias, predominantly sleepwalking, sleep terrors and RBD (Schenck et al., 1997). The mean age of onset in this group is younger than in typical RBD, at 15 years (range 1 to 66 years), but with a strong male predominance. In some patients the disorder is idiopathic; but in about one third of individuals it is associated with neurological disorders (such as narcolepsy, multiple sclerosis or brain tumour) or ethanol/ drug abuse or withdrawal. Another variant, *Narcolepsy-RBD*, has been described in which the two conditions develop in tandem (Schenck and Mahowald, 1992; Mayer, 1993). Treatment of cataplexy with tricyclic antidepressants in narcolepsy may induce or worsen RBD (Schenck and Mahowald, 1992). *Status Dissociatus* is the most extreme form of RBD, in which there is complete breakdown of normal state-determining boundaries (Mahowald, 1991). Patients will appear to be either awake or asleep, but their sleep is very atypical, both behaviourally (with twitching, vivid dreams and vocalizations) and polysomnographically, with loss of the normal REM and REM features. Sleep instead consists of an admixture of features of wakefulness, NREM and REM

sleep. This condition has been associated with alcohol withdrawal, olivopontocerebellar degeneration and brainstem lesions, and similar features are seen in familial fatal insomnia. (Schenck and Mahowald, 2002; Provini et al., 2004).

Pathophysiology. The underlying pathogenesis of RBD remains unclear, but it appears to arise through a failure of the mechanisms generating skeletal muscle atonia during REM sleep. A number of neural substrates participate in this process, any of which could potentially play a role in RBD. The most important site, however, appears to be the pons. Animal studies have demonstrated co-localisation of REM-atonia and locomotor systems in the pons (Lai, 1990), and a number of case reports support the association of pontine pathology and RBD (Barros-Ferreira, 1975; Plazzi, 1997). There is some evidence that the pedunculopontine and retrorubral nuclei may be implicated (Lai, 1990; Schenck, 1993), and the strong association with parkinsonism suggests that the dopaminergic system may be involved. The latter supposition has been supported by functional imaging studies in idiopathic RBD; striatal dopamine transporter binding is reduced in these individuals when compared to control subjects, although is significantly greater than in subjects with Parkinson's disease (Eisensehr, 2000).

Epidemiology. Chronic RBD mainly affects individuals over age 50 years (Schenck and Mahowald, 2002), with men affected in over 80% of large reported series (Schenck, 1993; Olsen, 2002). However, to date no major epidemiological studies have been undertaken to assess the incidence and prevalence of RBD in either the general population or within specific clinical populations (such as those with Parkinson's disease).

Recurrent Isolated Sleep Paralysis

Sleep paralysis is characterized by the absence of voluntary motor activity at the beginning or end of a sleep period. Patients are aware of their environment but feel completely paralysed, and may experience vivid hallucinations. The attacks are presumed to be a manifestation of REM sleep intrusion into wakefulness.

They usually last for only a few minutes and typically subside spontaneously, although may be aborted if the individual is touched (Sheldon, 2000). Sleep paralysis may occur in otherwise normal individuals, particularly after a period of sleep disruption or a change in sleep schedule (Takeuchi, 1992), but is also an extremely common feature of narcolepsy (Overeem et al., 2001). In the latter situation, other features such as excessive daytime sleepiness and cataplexy are also present. Unless narcolepsy is suspected, further investigation and treatment are not usually required.

Catathrenia

Catathrenia, or nocturnal groaning, is a recently described parasomnia consisting of recurrent moans and groans (Vetrugno et al., 2001). Each vocalisation lasts for 2 to 20 seconds each, and the groans often occur in clusters over a period of up to an hour. They may occur in both NREM sleep (predominantly stage 2) and REM, and are not associated with significant motor activity or sleep-disordered breathing. Patients are entirely unaware of the events, and bedpartners or parents usually initiate the medical consultation in this condition.

10.2.2 Sleep-related Movement Disorders

Periodic limb movements during sleep (PLMS)

Clinical Features. Periodic limb movements during sleep (PLMS) are characterised by repetitive and stereotyped movements of the legs, predominantly during NREM sleep. The typical movement is extension of the great toe and dorsiflexion of the ankle, often associated with flexion of the knee and hip; occasionally the upper limbs may be involved. They may be unilateral or bilateral, and occur quasi-periodically at intervals of about 20 to 40 seconds (Coleman, 1982); conventionally they are scored on polysomnography only if they are part of a series of four or more movements lasting 0.5 to 5 seconds with an intermovement interval of 4 to 90 seconds (ASDA, 2005). It is classified under the ICSD as a dyssomnia (a disorder causing either excessive sleepiness or insomnia), but there is considerable overlap between PLMS and restless legs

syndrome (RLS), a quasi physiological phenomenon present in up to 30% of those over 50 years of age (Bixler, 1982).

Pathophysiology. The pathophysiology of RLS and PLMS is not well established. There is evidence of a significant genetic contribution, with a family history being reported in around 50% of cases overall (Walters et al., 1996; Winkelmann et al., 2000) and autosomal dominant inheritance patterns in some families ; linkage to loci on chromosome 9p, 12q and 14q has been reported in the literature (Bonati et al., 2003; Chen et al., 2004; Ferini-Strambi et al., 2004; Winkelmann et al., 2005). There remains some debate as to the neural substrates for the condition, with some evidence favouring a peripheral basis but other evidence pointing towards spinal cord or brainstem origin. The dopaminergic system appears to be involved, with L-dopa and dopamine agonists improving the symptoms and constituting the mainstay of pharmacotherapy in these conditions (Stiasny et al., 2001; Hening et al., 2004), but supporting evidence from neuroimaging studies is relatively scanty. Brain iron deficiency is a potentially important, although currently unproven, mechanism in RLS and PLMS. Reduced ferritin and increased transferrin levels have been identified in the CSF of patients with RLS, even though serum levels may be normal (Earley et al., 2000; Mizuno et al., 2005); an MRI study has indicated reduced iron concentrations in the substantia nigra and putamen (Allen et al., 2001); and a recent large epidemiological study demonstrated significantly reduced soluble transferrin receptor concentrations (a marker of incipient iron deficiency) in this group of patients (Hogl et al., 2005). Furthermore, treatment with supplemental iron may resolve or improve the symptoms of RLS and PLMS (Nordlander, 1953; Kryger et al., 2002; Earley et al., 2004, 2005). Interestingly, iron plays several important roles in dopaminergic neurotransmission. It is a critical cofactor in dopamine synthesis, but also influences dopamine transporter, D_1 and D_2 receptor density and function; these are reduced in iron deficiency states (Youdim et al., 1980; Erikson et al., 2000; Erikson et al., 2001).

From a diagnostic perspective, however, while RLS and PLMS may cause significant sleep fragmentation with subsequent excessive daytime sleepiness, the nature of the movements rarely, if ever, results in diagnostic confusion with epilepsy.

Epidemiology. The prevalence of RLS has been estimated at 5.5% in the general population, with PLMS affecting around 4% (Ohayon and Roth, 2002). However, the prevalence of both conditions rises with age (Tan et al., 2001; Ulfberg et al., 2001) with one study reporting rates of RLS 3% in individuals under 30 years, 10% in those aged 30-79, and 19% in people over 80 years of age (Phillips et al., 2000). PLMS affects 80-90% of individuals with RLS (Montplaisir et al., 1997). Some studies have indicated higher rates of RLS in women (Rothdach et al., 2000; Ulfberg et al., 2001), although others have not confirmed this observation (Lavigne and Montplaisir, 1994; Phillips et al., 2000).

Sleep Bruxism

Bruxism, or teeth grinding, consists of grinding or clenching movements of the jaws during sleep which is noisy and can cause significant dental wear or temporomandibular joint pain. It is most common in children, but often persists into adulthood (Rugh, 1988), particularly in intellectually disabled individuals. The cause of bruxism is unknown, although in some individuals it may be precipitated or aggravated by drugs including SSRI antidepressants and levodopa (Magee, 1970; Ellison and Stanziani, 1993). Patients are usually unaware of the grinding, which occurs in NREM sleep (particularly stage 2), and often seek help due to complaints from a bed partner or because of dental problems. Treatment is required in individuals who have sustained significant dental damage, with splints often being the most useful treatment (Dylina, 2001). While bruxism rarely mimics epilepsy, it may be confused with faciomandibular myoclonus, which is characterized by frequent nocturnal myoclonic jerks of the masseter and orbicularis oris muscles of subcortical origin. The relationship between these disorders is unclear; indeed it is possible that several forms of sleep bruxism exist, resulting from more than one underlying mechanism, with faciomandicular myoclonus representing one subtype (Vetrugno et al., 2002).

Nocturnal leg cramps

This condition consists of painful, involuntary contractions of the leg muscles, arising suddenly during sleep or the transition from wakefulness to sleep. The

posterior quadrant of the leg and foot are most commonly affected, with the muscles palpably contracted and the feet and toes being held in extreme plantar flexion (Montagna, 2004). The cramps usually affect one side at a time, last from seconds to minutes, and resolve spontaneously or by forced dorsiflexion. They occur in all age groups, particularly the elderly and pregnant women. In some cases they may be related to electrolyte disturbances or other systemic illnesses (Abdulla, 1999), but often the cause is unknown (Montagna, 2000).

Rhythmic movement disorder (jactacio capitis nocturna)

This condition consists of stereotyped repetitive movements of the head and neck that occur at sleep onset and stage 1 sleep or during short arousals in light sleep (particularly stage 2, (Dyken, 1992). Head rolling from side to side is the most common movement, but headbanging may also occur; in some cases this may be violent enough to cause bruising or callus formation (Montagna, 2004). In some individuals, limbs or the whole body may be involved in the rhythmic movements; in some children body rocking (with the child on his or her knees) is the prominent movement. The behaviours last between a few seconds and 30 minutes, and are associated with varying degrees of awareness; some patients acknowledge a pleasurable aspect to them, whereas others are entirely unaware (Zaiwalla, 2005)

The condition is extremely common in very young children, particularly males. It occurs in up to 60% of infants at 9 months of age , but usually resolves early in childhood, with prevalence dropping to 5% by 5 years (Klackenberg, 1971); rarely it may persist into late childhood or adulthood, particularly in autistic or intellectually disabled individuals (Chisholm, 1996). It should not be confused with epilepsy, although the rarity of the condition in adulthood may occasionally lead to misdiagnosis in this age group.

10.2.3 Other (non-parasomnia, non-movement disorder) paroxysmal nocturnal events

Although the parasomnias discussed above are the main conditions which need to be distinguished from NFLE, a number of other motor conditions also warrant consideration in the differential diagnosis. These are classified under a number of headings in the ICSD-2, including sleep-related breathing disorders, isolated syndromes, normal variants and unresolved issues. For the sake of clarity they will be considered together in this review.

Sleep starts

Sleep starts, also known as hypnic jerks, are an extremely common phenomenon and are essentially physiological in nature. They consist of brief myoclonic jerks, usually affecting the whole body, at the transition of wakefulness to sleep. They are often associated with sensory phenomena, most commonly a sensation of falling. Caffeine, stress and excessive exercise may increase the frequency of jerks in some individuals. They rarely require investigation or treatment, although if very severe can cause sleep-onset insomnia, a condition known as excessive fragmentary hypnic myoclonus (Broughton, 1985; Vetrugno et al., 2002) which is listed as a proposed sleep disorder in the ICSD classification (ASDA, 2005). The physiological basis of these events is not well understood; while some authorities have suggested that they result from volleys of activity in the pyramidal tracts (Broughton, 1985), others have proposed that the principal disturbance is of sensory processing, with the motor activity a secondary phenomenon (Nielsen and Zadra, 2005).

Somniloquy

Sleep talking, or somniloquy, usually occurs during light NREM sleep or during arousals from deeper sleep, but occasionally arises during REM sleep (Aldrich, 1999). It is very common, particularly in children; one review of 600 sleep studies reported sleep talking in 13% of the studies (Rechtschaffen, 1962). It usually consists of single words or short sentences, usually with minimal affective content,

and is sometimes associated with body movement. Somniloquy may occur from any stage of sleep; while its cause is unknown, there appears to be a familial predisposition which it shares with other parasomnias such as somnambulism (Abe, 1984). It is sometimes associated with arousal disorders, obstructive sleep apnoea or REM behaviour disorder; however, unless the history is suggestive of one of these conditions, investigation and treatment is unnecessary.

Benign sleep myoclonus of infancy

This condition appears within the first month of life, and is characterised by clusters of brief, repetitive, synchronous, multifocal or generalised jerks of the limbs during NREM sleep (Coulter and Allen, 1982). Usually the upper limbs are affected, but occasionally the lower limbs are also involved. Neurological examination is normal, and the jerks usually resolve by two to four months of age. Transient immaturity of the serotonergic system has been proposed as a possible mechanism for this condition (Resnick et al., 1986).

Nocturnal psychogenic non-epileptic seizures (PNES)

In general events from sleep are unlikely to represent PNES, which arise from wakefulness. However, there is increasing evidence that PNES may be relatively common in apparent sleep ('pseudosleep') in which from a behavioural perspective the patient appears asleep, but on EEG shows signs of wakefulness such as eye blinks and a posterior dominant rhythm. Studies have indicated that between 12 and 58% of patients with PNES have events arising from apparent sleep (Thacker, 1993; Benbadis et al., 1996; Duncan et al., 2004). A history of sleep related events does not, therefore, preclude the diagnosis of PNES. However, PNES restricted exclusively to pseudosleep is very rare, with most affected individuals having events in both wakefulness and apparent sleep (Duncan et al., 2004).

Nocturnal panic attacks

Nocturnal panic attacks consist of recurrent awakening with a feeling of impending doom, often with tachycardia, sweating and choking; the symptoms are similar to panic attacks occurring during wakefulness (Craske and Barlow, 1989) They are relatively common amongst patients with panic disorder, with 44-71% reporting at least one such episode (Roy-Byrne, 1988; Mellman and Uhde, 1989). Patients nearly always experience daytime panic attacks as well, although a small subgroup have symptoms predominantly at night (Craske and Tsao, 2005). Most patients report nocturnal panic attacks to occur 1-3 hours after sleep onset, and they rarely occur more than once per night (Craske and Barlow, 1989). The episodes usually last 2-8 minutes, return to sleep is difficult, and vivid recall of the events is typical (Craske and Tsao, 2005). They are not generally associated with significant motor behaviours, with fear and autonomic features such as tachycardia, tachypnoea and diaphoresis predominating (Hauri et al., 1989; Mellman and Uhde, 1989). The underlying pathology is uncertain; while psychological factors are likely to be important, some authors have reported evidence of underlying disturbances of autonomic regulation in such patients (Sloan et al., 1999).

Sleep-related breathing disorders

As discussed above, there is increasing evidence that obstructive sleep apnoea may trigger arousal parasomnias (Guilleminault et al., 2003; Guilleminault et al., 2005). In addition, children with this condition may suddenly awaken and scream or cry following obstructive events (Carroll, 1995).

Gastroesophageal reflux

Sleep-related gastroesophageal reflux may result in recurrent awakenings from sleep, and usually presents with recurrent arousals with crying, vomiting, or epigastric pain (Wise, 2002). There is an association between reflux and respiratory problems, which may be the presenting feature (Sheikh, 1999).

Hypnic hallucinations

Although not strictly a motor disorder of sleep, hypnic hallucinations may occasionally cause diagnostic uncertainty. These hallucinations (termed 'hypnagogic' when occurring around sleep onset and 'hypnopompic' when around awakening) are associated with sleep-wake transition, and usually occur with partial awareness of the environment. They are common in the normal population, with up to 37% of the population reporting such events regularly (Ohayon et al., 1996). The most commonly reported hallucination is a sensation of falling, which occurs in 25% of people, and may be accompanied by a hypnic jerk. However, hypnic hallucinations are also frequently reported in narcolepsy, when they may be complex and vivid; intense visual or tactile elements are commonly reported, and the hallucinations are often terrifying for the patient (Bassetti, 2000).

Newly recognised conditions

A number of recently described conditions, categorized as 'isolated syndromes, apparently normal variants, and unresolved issues' in the ICSD-2, involve paroxysmal motor activity in sleep, generally at sleep onset. These conditions include arhythmic feet movements while falling asleep (Broughton, 1988), alternating leg muscle activation during sleep and arousals (Chervin et al., 2003), excessive fragmentary myoclonus (Broughton, 1985), propriospinal myoclonus at sleep onset (Vetrugno et al., 2001). These conditions consist of myoclonic jerks or excessive movements around the time of sleep onset, but as yet are not widely recognized and do not appear to be commonly confused with seizures.

Section 10.3: Differentiating Non-Epileptic Events in Sleep from Epilepsy

As discussed in Section 10.2, a wide range of conditions are characterized by paroxysmal motor activity during sleep. In reality, however, most do not cause diagnostic confusion with epilepsy. For example, the prolonged nature of conditions like bruxism and the characteristic description of periodic limb movements in sleep (PLMS) have little in common with the paroxysmal events which characterize nocturnal seizures. The predominant sources of confusion are episodes characterized by sudden arousal with motor activity and often dramatic or bizarre behaviours. The main disorders which present in this fashion are the NREM arousal parasomnias, REM sleep behaviour disorder, and nocturnal panic attacks.

10.3.1 Features of the clinical history

NREM Arousal Disorders vs NFLE

The NREM arousal disorders such as night terrors and somnambulism (Provini et al., 1999; Zucconi and Ferini-Strambi, 2000) cause the greatest diagnostic confusion with NFLE; distinguishing these conditions can be a major challenge for even the most experienced sleep physician or epileptologist. NREM arousal disorders are common in childhood, not uncommonly persist into adulthood, and often do not follow 'classical' patterns (Vaughn, 2002); it has been well recognized that some individuals diagnosed with parasomnias for years in fact had NFLE (Scheffer et al., 1994; Lombroso, 2000). Some authors have examined the differences between these conditions, and the clinical and electrographic features which may be useful in discriminating between them. These will be reviewed below. It should be noted, however, that papers with a complete and detailed description of arousal disorder episodes are scanty (Zucconi and Ferini-Strambi, 2000). Most descriptions of arousal disorders in the literature are not based on video EEG or PSG findings. In the few papers in which video monitoring has recorded events, usually only minor episodes with a limited resemblance to the patient's full blown attacks are seen, and only limited behavioural descriptions are

	Parasomnias (NREM arousal disorders)	NFLE
Age at onset	Usually < 10 years	Variable; usually childhood or adolescence
Positive family history	60-90%	up to 40%
Attacks per night (mean)	1 or 2	3 or more
Episode frequency/ month	<1 to 4	20-40
Clinical course (over years)	Tends to disappear by adolescence	Often stable with increasing age
Disease duration (mean)	Approx 7 years	Approx 20 years
Episode duration	Seconds to 30 minutes	Seconds to 3 minutes (often less than 2 minutes)
Semiology of movements	Variable complexity; not highly stereotyped (on video)	Highly stereotyped on video monitoring, often vigorous movements.
Trigger factors	Sleep deprivation, febrile illness, alcohol, stress	Often none identified
Associated conditions	Obstructive sleep apnoea	Often none identified
Ictal EEG	Slow waves, no epileptiform features	Often normal, or obscured by movement. Frankly epileptiform ictal rhythms in <10%
Time of episodes during sleep	First third of night, but usually after 90 minutes of sleep	Any time, but may occur in first 30 - 60 minutes
Sleep stage when events occur	NREM stage 3 or 4	Usually stage 2 NREM, occasionally stage 3 or 4

Table 10. 2. *Comparison of clinical and video EEG/PSG features of parasomnias versus NFLE (adapted from Provini et al. 1999 and Zucconi and Ferini-Strambi, 2000).*

given. As such, many of the features attributed to NREM arousal parasomnias are based largely on clinical impressions. In addition there is the definite possibility, particularly in older studies performed before nocturnal frontal lobe epilepsy was well recognized, that some descriptions of parasomnias may have in fact referred to patients with NFLE (Scheffer et al., 1994). The features said to b important discriminators between NFLE and NREM parasomnias are discussed below and summarized in Table 10.2.

(i) Age of onset and persistence into adulthood. Both NFLE and arousal disorders usually first appear in the paediatric population. Overall, parasomnias tend to appear at a somewhat earlier age than frontal lobe seizures, with onset often in early childhood. Prevalence of night terrors peaks at 5-7 years of age (Kales et al., 1980; Zucconi and Ferini-Strambi, 2000); somnambulism usually presents a little later, with a peak prevalence at age 10 (Montagna, 2000). In contrast, in the largest series of NFLE patients reported, the mean age of onset was 14 years (Provini et al., 1999). However, in both groups the range is wide. Sleepwalking has been reported to begin after age 14 years in up to 10 % of cases (Hublin et al., 1997), and in one study of 13 patients with troublesome arousal disorders recorded on PSG, the mean age of onset was 13.5 years (Zucconi et al., 1995). In the NFLE series quoted above, age of onset ranged from 1 year to 64 years. Thus, while onset in later childhood or adolescence is more typical of NFLE than parasomnias, the great variability in the presentation of both conditions limits the discriminatory value of this parameter.

A number of authors have also described the persistence of events into adulthood as a possible indicator of an epileptic aetiology (Provini et al., 1999; Zucconi and Ferini-Strambi, 2000). The mean lifetime duration of somnambulism is only 7 years (Sours, 1963), with the majority of sleepwalkers remitting before 18 years of age (Cirignotta, 1983), whereas the mean lifetime duration of NFLE was 20 years in Provini et al's study. However, arousal disorders in adults are not uncommon, being seen in up to 4% of the population (Hublin et al., 1997). Although the exact prevalence of NFLE is unknown, it is considerably smaller than this. While persistence into adulthood may be a typical characteristic of NFLE, the high

prevalence of arousal disorders in the community means that the majority of individuals with sleep related events persisting into adulthood are likely to have parasomnias. Moreover, this feature is of little value for the clinician when it comes to making a diagnosis in a child or adolescent.

(ii) Frequency and clustering of events. The arousal disorders characteristically occur quite infrequently, typically 1-3 times per month on average (DiMario and Emery, 1987; Zucconi and Ferini-Strambi, 2000), but there are few large scale studies in this area. It is recognized, however, that they can occur on a nightly basis (Guilleminault et al., 2003), and unusually may occur more than once per night (Provini et al., 1999). On the other hand, frontal lobe seizures very commonly occur in clusters, with many events occurring on a single night. On average, individuals will experience 3 to 8 events in one night, usually in the space of a few hours (Provini et al., 1999; Berkovic, 2002)\, but some patients report 20 or more seizures per night. Overall, in Provini's series the mean number of reported seizures per month was 20, significantly more than is usually seen in arousal disorders (Sours, 1963; Montagna, 2000).

(iii) Timing of events. Disorders of arousal arise from deep NREM sleep (stage 3 or 4, slow wave sleep) (Montagna, 2000; Niedermeyer and Lopes da Silva, 2004). As a result, these episodes are not usually seen until the patient has been asleep for some time, typically 90 minutes to 2 hours after sleep onset. They most commonly occur within the first third of the sleep period, during the longest consolidated period of slow wave sleep (Zucconi and Ferini-Strambi, 2000). In contrast, seizures in NFLE usually arise from stage 2 NREM sleep (Crespel et al., 1998; Provini et al., 1999). This is born out by historical accounts, in which seizures are reported to occur at any time but most commonly within 30 minutes of sleep onset (Berkovic, 2002).

(iv) Behaviours during events. The behaviours reported in NREM arousal disorders and NFLE are discussed in detail elsewhere in this review. The motor patterns observed during these events, such as wandering, semipurposeful

automatisms and motor agitation, may be seen in both conditions, and there are few if any specific features which discriminate between the conditions (Zucconi and Ferini-Strambi, 2000). However, the prominent stiffening and dystonic posturing often seen in NFLE is unusual in the arousal disorders (Provini et al., 1999).

(v) Duration of events. Parasomnias are usually described as relatively prolonged events, usually over 5 minutes in duration (Provini et al., 1999; Zucconi and Ferini-Strambi, 2000), although they may be briefer than this (Zaiwalla, 2005). Whilst individual episodes may be reported which last for less than 1 minute, the individual's typical attacks often persist for much longer, occasionally up to 30 minutes (Aldrich, 1999). In contrast, the events seen in NFLE are brief. Provini et al recorded 660 nocturnal frontal lobe seizures in 100 patients; the vast majority of events lasted for less than 2 minutes and the longest recorded seizure was 3 minutes in duration (Provini et al., 1999). As previously discussed, frontal lobe seizures have been subdivided into paroxysmal arousals, paroxysmal nocturnal dystonia and epileptic nocturnal wandering (Montagna, 1992). Only epileptic nocturnal wanderings have been reported to last over 2 minutes and this seizure type is relatively uncommon, constituting less than 3% of events in NFLE (Provini et al., 1999).

(vi) Stereotypy. NREM arousal disorders may be broadly stereotyped within an individual, but there is usually some variability in the behaviours observed in individual events. In contrast, seizure of NFLE are highly stereotyped, with smaller events representing fragments of larger seizures (see Chapter 8, page 142).

(vii) Recall. Subjects are unaware of their surroundings during parasomnias; in most instances they will return to restful sleep after the event without waking, and will have no recollection of the event the following day (Aldrich, 1999; Montagna, 2000; Zaiwalla, 2005). Some individuals, however, report vague, poorly formed memories of frightening dreams (Schenck and Mahowald, 1995) or a partial recollection of the episode intermingled with dream mentation (Aldrich, 1999).

On these occasions, the subject usually does not remember the onset of the event, but may have a hazy and dream-like recollection of the moments shortly before full waking. In contrast, awareness may be retained during frontal lobe seizures. Many individuals, particularly those with autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE), are woken from sleep with a characteristic aura, most commonly a sensation of dyspnoea or choking (Scheffer et al., 1995). Individuals with NFLE often have a clear recollection of at least some of their events and can often give clear descriptions.

(viii) Vocalisation. Vocalisation is common in both NFLE and parasomnias. Shouting, screaming and incoherent speech may occur in either condition, and therefore these features are not helpful in discriminating between them. Coherent speech, however, is a more useful feature. Coherent speech in NFLE is usually a feature of the retained awareness and speech content is recalled by the patient (Williamson, 1995). In parasomnias, speech is conducted while the patient is unaware and the patient will usually have no recall of any conversation the following day (Sheldon, 2004). Some subjects may wake during the events and have some recall of end of their conversation the following day, and others may have a dreamy partial recollection of a conversation, but clear and complete recall of speech is very uncommon in a parasomnia.

Overall, the most consistently identified clinical features for discriminating between NFLE and parasomnias are: frequency of events, timing of events during sleep, and the duration of individual events (Provini et al., 1999; Zucconi and Ferini-Strambi, 2000). A number of other features said to be useful may in fact have less practical value. For example, a positive family history is common in parasomnias but may also be seen in ADNFLE (Scheffer et al., 1995); and the triggering of events by disrupted sleep or stress is said to be very common in parasomnias, but may also contribute to the provocation of seizures (Zucconi and Ferini-Strambi, 2000). Overall, despite some suggestive features, the differentiation of these disorders on the basis of the history alone can be difficult. All authors stress the importance of recording episodes by way of video EEG/PSG

to confirm the diagnosis (Roberts, 1998; Provini et al., 1999; Zucconi and Ferini-Strambi, 2000). This raises logistical problems in individuals with irregular or infrequent events, and in regions where this service is not readily available.

RBD vs NFLE

While REM sleep behaviour disorder may have some superficial similarities to NFLE, its clinical course is usually quite different.

a)Age of onset. The most important difference between NFLE and RBD from a diagnostic point of view is its tendency to develop in older individuals; the mean age of onset is 52-62 years (Schenck, 1993; Sforza et al., 1997; Olsen, 2002), and it is uncommon in children (Sheldon and Jacobsen, 1998). This is clearly in contrast to both nocturnal frontal lobe epilepsy and NREM arousal disorders which usually appear in the paediatric age group (Aldrich, 1999; Provini et al., 1999).

b) Association with neurological diseases. The strong association of RBD with neurodegenerative disorders (particularly Parkinson's disease and Multiple System Atrophy), as well as other neurological conditions such as narcolepsy, is in marked contrast to individuals with NFLE who almost always have normal neurological examination and neuroimaging (Provini et al., 1999).

c) Altered dream patterns, dream enactment and sleep-related injury. Almost 90% of individuals with RBD complain of intense, vivid, and often violent dreams, which are qualitatively different to their premorbid dreams. A similar number have 'oneieric', or dream enactment, behaviours with swearing, punching, kicking, jumping out of bed and running. These often result in injury to the patient or bed partner, which is often the presenting complaint in RBD (Schenck and Mahowald, 2002). In contrast, dream quality does not change with the onset of NFLE. While seizures may involve behaviours such as vocalization, running and jumping, they are not associated with dreaming; they are either not remembered at all, or occur with genuine recollection of the event. Injury may

occur during nocturnal frontal lobe seizures, but is not widely reported, and is rarely the presenting complaint (Schenck et al., 1989).

d) Duration of event and rousability. The events of RBD are of variable duration, but individuals are generally rousable, being woken by their bedpartner, collision or injury. In contrast, the events of NFLE are in the main very brief, but cannot be terminated by external stimuli.

e) Stereotypy. As discussed previously, the seizures of NFLE are highly stereotyped, but this is not the case in RBD. In the latter case, behaviours of the patient reflect the dream content, which usually varies from night to night. Furthermore, multiple non stereotyped minor behaviours often occur throughout sleep, such as twitches, groans, sleep talking and gross limb jerks (Schenck, 1986; Schenck and Mahowald, 2002), often preceding the development of overt RBD.

Nocturnal panic attacks vs NFLE

Although nocturnal panic attacks share a number of clinical features with nocturnal frontal lobe epilepsy they should rarely be a source of significant diagnostic confusion. From the perspective of diagnosis, the most important feature of nocturnal panic is the coexistence of panic disorder and daytime panic attacks (Craske and Tsao, 2005). Nocturnal panic attacks in these individuals are not significantly different to daytime panic attacks, being characterised by fear and autonomic features such as tachycardia and sweating (Craske and Barlow, 1989); they will usually be recognised as panic attacks by the patient who is fully aware throughout (Craske and Tsao, 2005). They are predominantly affective phenomena without significant motor activity , are relatively prolonged, lasting 2-8 minutes on average, and rarely occur more than once in a night (Craske and Barlow, 1989; Craske and Tsao, 2005).

However, the presence of retained awareness and subjective feelings of choking and breathlessness may present some diagnostic difficulty in the rare individual with exclusively nocturnal events, particularly if they are of brief duration.

10.3.2 Features of video EEG/PSG monitoring

In cases of diagnostic doubt, video EEG or video EEG-PSG monitoring may be the only way of accurately distinguishing NFLE from other paroxysmal motor disorders of sleep.

Video EEG findings in NFLE

The video EEG findings in NFLE have been well described (Provini et al., 1999) and are reviewed in detail in Chapters 7 and 8. By far the most common seizure type is the paroxysmal arousal, constituting 75% of the recorded seizures; paroxysmal nocturnal dystonia constitute a further 23%, and epileptic nocturnal wanderings make up only 2% of recorded seizures. Most patients have at least two of these seizure types identifiable on monitoring, and autonomic features such as tachycardia and irregular respiration are often prominent. Although individuals with NFLE may have events of varying duration and complexity, brief attacks tend to represent fragments of the larger seizures (Provini et al., 1999). The onset patterns of these events is usually strikingly stereotyped (Provini et al., 1999), a finding that can be clearly seen by the use of split-screen video EEG-PSG (Tinuper et al., 2004; Valenti et al., 2006). Stereotypy may not be invariably the case, however; a recent intracranial electrode study indicated that in some patients with NFLE, the semiology of brief epileptic paroxysmal arousals may be different in individual events (Nobili et al., 2005).

Electrographically, events occur almost invariably during NREM sleep, with about 70% occurring in stage 1 or 2. Interictal EEG is usually normal, with clear-cut epileptiform discharges present in only 33% of individuals in wakefulness and 45% in sleep. Ictal EEG shows no epileptiform activity in almost 50%; in the majority of those which do show abnormalities, focal attenuation or rhythmic theta or delta is the prominent rhythm; only around 10% will show spike and wave activity, and another 10% show focal fast activity.

Video EEG in Arousal disorders

Video EEG and video PSG recording of these disorders is often not possible due to their infrequent or unpredictable occurrence, and there are relatively few well documented series in the literature (Zucconi and Ferini-Strambi, 2000). Often during a monitoring period the events recorded are minor compared to the usual episodes, or they do not occur at all. As a result there are very few clear descriptions of semiology from video monitoring in the literature; most reported events are characterised by little more than the patient sitting up, looking around and vocalizing (Kavey et al., 1990; Espa et al., 2002). Most patients do not leave the bed in the laboratory; often they are restricted by the EEG electrodes and lie back down to sleep (Kavey et al., 1990).

Electrographically, events usually occur in the first part of the night, arising from slow wave NREM sleep (i.e. stage III or IV (Gastaut, 1965; Kavey et al., 1990; Pressman et al., 1995; Espa et al., 2002). Classically, a combination of alpha, delta and theta frequencies is seen, without evidence of clear wakefulness (Jacobson, 1965). Sometimes a non-reactive posterior alpha pattern is seen (described by Gastaut and Broughton as substage 1a3), which gives a picture of mixed awake and asleep rhythms (Gastaut, 1965). In individuals with sleep terrors there may be rapid desynchronisation or low voltage waking patterns, often combined with increased heart rate, tachypnoea, and increased muscle tone. During somnambulism, light sleep patterns (stage 1) are often seen. Importantly, epileptiform activity is not present during these episodes (Niedermeyer and Lopes da Silva, 2004).

Video EEG/PSG in RBD

The diagnosis of RBD is usually confirmed using video-polysomnographic monitoring. According to the International Classification of Sleep Disorders (ASDA, 2005) one of the following findings during REM sleep confirms RBD: either excessive augmentation of chin EMG tone; or excessive chin or limb phasic twitching (irrespective of the chin EMG activity), with jerking or complex behaviours and without epileptic activity. Normal sleep architecture is preserved

(Schenck, 1993; Olsen, 2002). Frank events may be recorded during REM sleep on video EEG or PSG monitoring, with violent limb movements such as flailing, punching or kicking; simple or complex behaviours (such as waving, pointing, searching or reaching) corresponding to dream activity; and prominent vocalization including laughing, talking moaning and chanting (Schenck, 1986). The timing of events in the sleep cycle (REM sleep vs stage 2 NREM for seizures), in conjunction with the nature of the observed behaviours and the observation of preserved EMG tone during REM sleep, should result in a relatively straightforward diagnosis in most cases. Epileptiform activity is not seen during these events.

Video EEG/ PSG in nocturnal panic attacks

On nights without panic attacks, patients with nocturnal panic show PSG and EEG parameters which are similar to those of control subjects, although they may have slightly longer sleep latencies and increased movement during sleep (Hauri et al., 1989; Landry et al., 2002). Panic attacks usually arise from stage 2 or 3 NREM sleep, often around the time of sleep stage transition (Lesser et al., 1985; Hauri et al., 1989). Subjects have only single events in any monitored night, often have a prolonged sleep latency after the attack (up to 2 hours), and have vivid recall of the event the following day (Hauri et al., 1989). In some individuals, some observable features of the events, such as tachycardia and movement, appear during sleep, but in others these features were only seen after waking.

Conclusion

There are many non-epileptic disorders characterized by motor activity in sleep. From a practical perspective, it should usually be possible for the clinician to accurately identify these on the basis of the clinical history,. However, NFLE may present in a very similar fashion to some of these, particularly the NREM arousal parasomnias; it may be difficult or impossible for even very experienced epileptologists and sleep physicians to make a definite diagnosis. Interical EEG, PSG and cerebral imaging may be useful in some individuals, but these investigations are frequently non-contributory. In such cases the recording of

episodes using video EEG- PSG may be required to make a definite diagnosis, although this may be difficult to achieve. Moreover, in many sleep disorders, most notably the NREM arousal parasomnias, comprehensive video EEG/PSG studies are still lacking. As the EEG may be non-contributory in both NFLE and parasomnias, , diagnostic doubt may remain even after the recording of events.

From a biological perspective, the understanding of sleep disorders is still in its infancy. The current understanding of underlying mechanisms is usually based upon data from small case series or single cases, and is often highly speculative. Moreover, in many cases the conditions themselves may represent extremes of normal physiology. For example, periodic limb movements in sleep and arousal parasomnias are seen so frequently in the general population that they cannot be considered as pathological in their own right; such conditions only become a 'disorder' when they result in distress, injury or harm to the individual or others. Detailed further study in this area is therefore warranted, not only to understand these conditions *per se,* but also to provide insights into the process of sleep itself.

PART 2:- STUDIES

CHAPTER 11

Serotonergic Neurotransmission in Human Sleep: Evidence from an ^{18}F-MPPF Study

Introduction

The neurochemical changes which underpin human sleep may play a key role in the precipitation of seizures in some epilepsy syndromes. Serotonin, interacting with other neurotransmitters such as acetylcholine and noradrenalin, appears to promote wakefulness and suppress REM sleep. The serotonergic system is phylogenetically ancient, and is found in all mammalian species. The majority of serotonergic cell bodies are located in the raphe nuclei, which lie around the midline of the brainstem, but these have widespread projections throughout the brain. Previous animal studies have suggested that the system is a fundamental component in the neurochemical regulation of sleep. Activity demonstrated with single unit recordings from serotonergic neurons in the dorsal raphe nucleus (McGinty and Harper, 1976; Trulson and Jacobs, 1979; Cespuglio et al., 1981) is tightly linked to the stage of sleep. The neurons are active in wakefulness, becoming progressively less active during non-REM sleep, and are essentially quiescent during REM sleep. Microdialysis studies in cats and rats (Portas and McCarley, 1994; Portas et al., 1998; Park et al., 1999; Strecker et al., 1999) have demonstrated changes in serotonin concentration which parallel the changes in neuronal firing rates (see Chapter 2 page 45-6 for further details).

Most available information about changes in serotonergic neurotransmission through the sleep-wake cycle has been obtained in experimental animals. There are dangers in extrapolating this to humans given our knowledge of interspecies differences. For example, serotonin exerts dramatic modulatory effects on circadian rhythms in hamsters but not mice (Antle et al., 2003), and lesions of the dorsal raphe nucleus have been shown to reduce sleep in cats (Jouvet, 1972) but not in rats (Bouhuys and Van Den Hoofdakker, 1977). The only human data on serotonin release during the sleep-wake cycle to my knowledge is a single case report showing that the serotonin concentration in the CSF from the lateral

ventricles was greatest in wakefulness and lowest in REM sleep (Zeitzer et al., 2002).

Aim and Hypothesis

Aim

In light of the paucity of human data, the aim of this study was to evaluate endogenous serotonin release in wakefulness and sleep in human subjects using the $5HT_{1A}$ PET ligand [^{18}F]MPPF.

Hypothesis

[^{18}F]MPPF binding is greater in sleep than in wakefulness, reflecting a reduction in endogenous serotonin release during sleep.

Methods

This study comprised two sections, a human study (Part 1) and an animal study (Part 2).

Part I: Effect of sleep on [^{18}F]MPPF binding: Human study

Subjects. One of the problems faced by functional neuroimaging studies of human sleep is the lack of predictability with which spontaneous sleep occurs. Patients with narcolepsy were studied here as a way of circumventing this problem. Fourteen subjects with a diagnosis of narcolepsy (12 females, 2 males; median age: 55 years; age range: 26-67 years) were studied. The clinical features of the subjects are described in Table 11.1. The following inclusion criteria were applied: age over 18 years; diagnosis of narcolepsy made by a consultant neurologist following appropriate investigation; treatment with either methylphenidate alone or no medication. Subjects were excluded from the study if they had taken neuroleptic, antidepressant or stimulant medication other than methylphenidate within 1 month of enrolment; if there was a history of other neurological or psychiatric illness; or if the subject was pregnant. Subjects underwent a medical interview prior to enrollment in the study. In view of the

potential effects of mood and serum tryptophan on endogenous serotonin release, all subjects completed the Beck Depression Inventory (BDI) and the Beck Anxiety Inventory (BAI) on the day of each PET scan. They were supplied with standardized meals for 24 hours prior to each scan (no caffeinated drinks were permitted during this period), and serum tryptophan levels were measured 30 minutes prior to each scan. All subjects gave their written informed consent to the study protocol, which was approved by the medical ethics committee of the Austin Hospital.

Radiochemistry. Tracer synthesis was performed by Rachel Mulligan and Henri Tochon-Danguy in the Deprtment of Nuclear Medicine, Austin Hospital, Melbourne. [^{18}F]MPPF was obtained by nucleophilic substitution of the aromatic nitro group using previously described methods (Le Bars et al., 1998). The purity of [^{18}F]MPPF was greater than 99% on each synthesis, and specific activity ranged from 873-3300 mCi/μmol.

PET. Each patient underwent two [^{18}F]MPPF scans (total injected dose 4mCi), one whilst taking their usual doses of methylphenidate (during which the subject was required to stay awake), and one after the subject had omitted methylphenidate on the day of the scan (during which the subject was allowed to fall asleep in the scanner prior to tracer injection). Each scan was carried out with polysomnographic monitoring (EEG, EOG and EMG) to monitor sleep state during the acquisition period. The PET scans were performed between 2 and 3 pm in every case, with the two scans being performed 1 week apart. Dynamic PET scans comprising 26 frames were acquired over 60 minutes using an ECAT positron tomograph (951/31R, CTI Siemens, Knoxville, TN, USA). The scanner was operated in 3D mode. Head movement was minimized using a moulded head-rest and head restraint. The data were reconstructed using the Kinahan and Rogers 3D reprojection algorithm (Kinahan, 1989) with a Hanning filter. Attenuation correction was performed using data from a 10 minute transmission scan with gallium-68 /germanium -68 sources. The final image comprised 128x128x31 slices where the pixel size was 2.34mm and the slice thickness was 3.37mm.

Sex	*Age (years)*	*Methylphenidate dose (mg/day)*	*%age of time spent in sleep*		*Classification*	*Mean [^{18}F]MPPF BP (Whole Brain)*	
			Wake scan	Sleep scan		Wake scan	Sleep scan
M	51	30	0	84	Good Sleeper	0.223	0.241
F	54	45	3	93	Good Sleeper	0.196	0.240
F	62	30	0	87	Good Sleeper	0.188	0.212
F	59	90	0	85	Good Sleeper	0.237	0.283
F	27	40	0	93	Good Sleeper	0.318	0.349
F	26	Nil	0	84	Good Sleeper	0.238	0.278
F	35	Nil	0	89	Good Sleeper	0.272	0.276
F	66	30	0	19	Poor Sleeper	0.228	0.234
F	56	50	0	34	Poor Sleeper	0.212	0.199
F	29	50	0	21	Poor Sleeper	0.191	0.194
M	52	10	8	26	Poor Sleeper	0.235	0.264
M	66	70	0	29	Poor Sleeper	0.265	0.265
F	58	70	0	52	Poor Sleeper	0.224	0.212
F	67	40	0	30	Poor Sleeper	0.284	0.281

Table 11. 1. *Summary of clinical and treatment information for subjects in the study, with details of sleep duration in 'wake' and 'sleep' scans*

MRI. MRI acquisition consisted of a high resolution three-dimensional T1 - weighted image comprising 120 contiguous slices of 1mm thickness and 1mm x 1mm pixel dimensions, with the anatomical volume covering the whole brain. MRI scans were acquired on a 1.5T Signa Echospeed Superconducting Imaging System (General Electric Medical Systems, Milwaukee, WI). The three dimensional spoiled gradient recalled echo acquisition comprised TR 10.5 milliseconds, TE 2.2 milliseconds, TI 350 milliseconds, flip angle 20 degrees, FOV 25cm, matrix 256 x 256, NEX 1.

Data analysis

Kinetic Analysis. A parametric image, obtained by estimating the binding potential (BP) and K_1 ratio (R_0) for each voxel, was generated for each PET dataset using a simplified reference tissue model (Lammertsma and Hume, 1996) validated for MPPF studies (Passchier et al., 2001). This model derives BP from the ratio of the volumes of distribution of the ligand in the region of interest relative to the cerebellum, which has been shown to be devoid of $5HT_{1A}$ specific binding (Burnet et al., 1995; Hall et al., 1997). No arterial sampling was performed, and K_1 was not directly measured. The cerebellar region of interest was manually drawn on MRI images using interactive mouse driven software. These MRI images had previously been registered to an image comprising the sum of all frames from the dynamic PET acquisition. Linear registration was performed using AIR (Woods et al., 1992) yielding a 9 parameter transformation matrix for translation, rotation and scaling along each of the principal axes.

Whole brain BP and K_1 ratio (R_0) values. Mean whole brain BP values were obtained after transformation of the images to a common stereotaxic coordinate space. This allowed the application of a common whole brain mask for each pair of sleep and waking scans. The mask was created using a standard template which included the whole brain apart from the reference region. Because the field of view of the positron emission tomograph used in this study did not incorporate the entire cerebrum, to correct for subtle differences in patient position between scans, only voxels imaged in both the sleep and wake states were included in the mask.

Regions of Interest. In sleep and waking scans, mean values for BP and R_0 were calculated for ROIs drawn on the same MRI images that were used for the cerebellar ROI. Because of their potential importance in the regulation of the sleep-wake cycle or because of the high content of 5HT1A receptors, the following regions were selected: anterior cingulate gyrus, mesial temporal region (hippocampus and amygdala), and temporal cortex (temporal pole, parahippocampal gyrus and temporal neocortex). Regions of interest incorporating the raphe nuclei were not examined because of the difficulty in accurate anatomical delineation on MRI scans and the potential errors in parameter estimates relating to partial volume effect and the small size of the nuclei.

Polysomnographic Analysis. Duration of sleep during the scanning period was encoded from the polysomnographic data which were reviewed and staged according to the classification system of Rechschaffen and Kales (Rechtschaffen, 1968). Scoring was undertaken by the author prior to PET data analysis, and therefore blind to the PET results. The polysomnographic data were used to divide the subjects into (i.) 'good sleepers', who slept > 75% of total scan time and (ii.) 'poor sleepers', who slept < 75% of total scan time.

Statistical Analysis.

Change in BP in sleep wake cycle. The paired Student's t-test was used to compare mean BP in the whole brain and in individual ROIs in sleep and wake scans for the entire group. This analysis was then performed separately for the 'Good Sleepers' group and the 'Poor Sleepers' group.

Second, the change in BP between wake and sleep scans (ΔBP) was calculated using the following formula:

$$\Delta BP = 100 \times \frac{BP_{\text{sleep scan}} - BP_{\text{wake scan}}}{BP_{\text{wake scan}}}$$

The unpaired t-test was then used to compare mean ΔBP in the population of 'Good Sleepers' vs 'Poor Sleepers'.

Change in K1 ratio (R_0) in sleep wake cycle. To assess whether BP changes were associated with changes in tracer delivery as reflected by R_0, the analyses above were repeated for the R_0 and for ΔR_0:

$$\Delta R_0 = 100 \times \frac{R_{0\text{sleep scan}} - R_{0\text{wake scan}}}{R_{0\text{wake scan}}}$$

Influence of other variables. To assess whether affective state (BDI and BAI scores), serum tryptophan values, ΔR_0 and methylphenidate dose were related to ΔBP, these additional variables were included in a multivariate stepwise regression analysis.

Part II: Effect of methylphenidate on [^{18}F]MPPF binding (β-microprobe study)

To assess the possible impact of treatment with methylphenidate, changes in [18F]MPPF binding were examined following administration of methylphenidate in rats using an intracerebral β-sensitive detector (the β-microprobe; Zimmer et al., 2002). Previous studies have shown this technique to be reliable in detecting changes in [^{18}F]MPPF binding correlated with changes in endogenous serotonin release (Zimmer et al., 2002; Rbah et al., 2003; Zimmer et al., 2003; Riad et al., 2004). The author designed and assisted in the experiments which were conducted under the direction of Didier Le Bars and Luc Zimmer at CERMEP Biomedical Cyclotron, Lyon France.

Radiochemistry. Radiosynthesis was undertaken by Didier le Bars at CERMEP, Biomedical Cyclotron, Lyon, France. The radiochemical purity of [18F]MPPF was greater than 95% on each synthesis, and specific activity ranged from 74 x 10^3 MBq/μmol to 148 x 10^3 MBq/μmol (2-4 Ci/μmol).

Animals. 5 adult male Sprague Dawley rats (250±50g body weight; Charler River, L'Arbresle, France) were housed at a constant temperature and with *ad libitum*

access to food and water. All procedures involving animals and their care abided by the regulations of the European Economic Commission (86/09/EEC) and were approved by the Animal Care Committee at the Claude Bernard University. As described in detail previously (Zimmer et al., 2002), after anesthesia with urethane (1.7gm/kg, i.p.), each rat was positioned in a stereotaxic frame on a thermostatically controlled heating blanket (37±1 C), and a catheter was inserted into the tail vein to allow subsequent injection of the radiotracer. Two β-microprobes were then implanted under stereotaxic control; one in the cerebellum and one in the hippocampus. The sensitive end of the probe consisted of a plastic scintillating fiber that was 1mm in length and 1mm in diameter. The sensitivity of the probes, measured *in vitro* is close to 0.55 measured counts per kilobecquerel per milliliter. According to previous Monte Carlo simulations, the probe detection volume is defined as a 1.3 mm radius sphere centered on the probe end corresponding to 90% of the recorded signal.

Methylphenidate treatment and [^{18}*F]MPPF binding kinetics.* [^{18}F]MPPF injections were performed 2 hours after implantation of the probes. For each acquisition, 2mCi [^{18}F]MPPF was injected over a 45 second period. The course of radioactivity was studied for 180 minutes in the hippocampus and cerebellum, using a 10 second time integration acquisition. At 20 minutes after [^{18}F]MPPF administration, each rat received an injection of methylphenidate at 15mg/kg, a dose at which clear behavioral effects have been observed in rats, and which is significantly larger than that used therapeutically in humans. After protocol acquisition, the anaesthetized rats were killed and their brains quickly removed and frozen at -80°C. Coronal sections were cut and probe placements were atlas matched.

Data analysis. The raw data were expressed as mean number of disintegrations (Zimmer et al., 2002) per 10 seconds, averaged at 1 minute intervals and corrected for radioactive decay. Analysis was conducted comparing means obtained from previously acquired control data with methylphenidate-treated rats.

Results

Part 1: Human Study

Of the 14 subjects studied, 7 slept for greater than 75% of the study ('Good Sleepers') and 7 slept for less than 75% of the scan time ('Poor Sleepers').

Change in BP in sleep wake-cycle. The values for mean BP change in whole brain and each ROI are presented in Table 11.2. Mean BP in whole brain and all ROIs was significantly greater in sleep than in wakefulness for the group as a whole. This difference was more pronounced in 'Good Sleepers'; mean parametric images in wakefulness and sleep from the population of 'Good Sleepers' are shown in Figure 11.1. In contrast, no significant difference was seen between sleep and wake scans in the 'Poor Sleepers' group. ΔBP was significantly greater in 'Good Sleepers' than in 'Poor Sleepers' in the whole brain and in all ROIs except the mesial temporal region (Figure 11.1).

Change in K_1 ratio (R_0) in the sleep wake-cycle. No significant change in R_0 was seen in the whole brain either in the group as a whole or the 'Good Sleepers'. However a small but statistically significant increase in R_0 during sleep was seen in some regions of interest. In the group as a whole, the mean increase in R_0 was 0.04 in the cingulate ROI and 0.03 in the mesial temporal ROI ($p<0.05$ for both). This finding was also seen when only the 'Good Sleepers' were examined (increase in R_0 in cingulate: 0.08, $p<0.01$; in mesial temporal ROIs: 0.04, $p<0.01$). In this group there was also an increase in R_0 in the temporal neocortex of 0.03 ($p<0.05$). ΔR_0 was not significantly different in 'Good Sleepers' compared to 'Poor Sleepers' in the whole brain ($p = 0.3$) or in any ROI. There was no correlation between ΔR_0 and ΔBP ($r = 0.27$, $p = 0.4$).

Influence of other variables besides sleep. Measures of mood and serum tryptophan concentration were found to be similar in the sleep and wake scans. The median BDI score for the wake scan was 4 (range 0-16), and for the sleep scan was 3 (range 0-12). The median BAI score for the wake scan was 5 (range 0-

Brain Region	*Mean increase in [^{18}F]MPPF BP in sleep scan compared to wake scan (± SD)*		
	All subjects (n=14)	**'Good Sleepers' (n=7)**	**'Poor Sleepers' (n=7)**
Whole Brain	0.016 (± 0.02)*	0.030 (± 0.01)**	0.001 (± 0.01)
Cingulate Gyrus	0.045 (± 0.06)*	0.092 (± 0.04)**	0.000 (± 0.05)
Mesial Temporal	0.092 (± 0.14)*	0.160 (± 0.14)**	0.024 (± 0.09)
Temporal Cortex	0.034 (± 0.04)*	0.056 (+/- 0.04)**	0.011 (± 0.03)

Table 11. 2. *Mean difference in BP in sleep and wake scans in whole brain and individual ROIs; values are given for the whole group, and the groups of 'good sleepers' and 'poor sleepers'. The differences in BP have been analyzed using paired t tests and are statistically significant in all regions in the 'All subjects' group and to a larger extent in the 'Good sleepers' group. In contrast, no significant difference between BP in the sleep and wake scans is seen in the 'Poor sleepers' group.*
** significant at p<0.05*
*** significant at p<0.01*

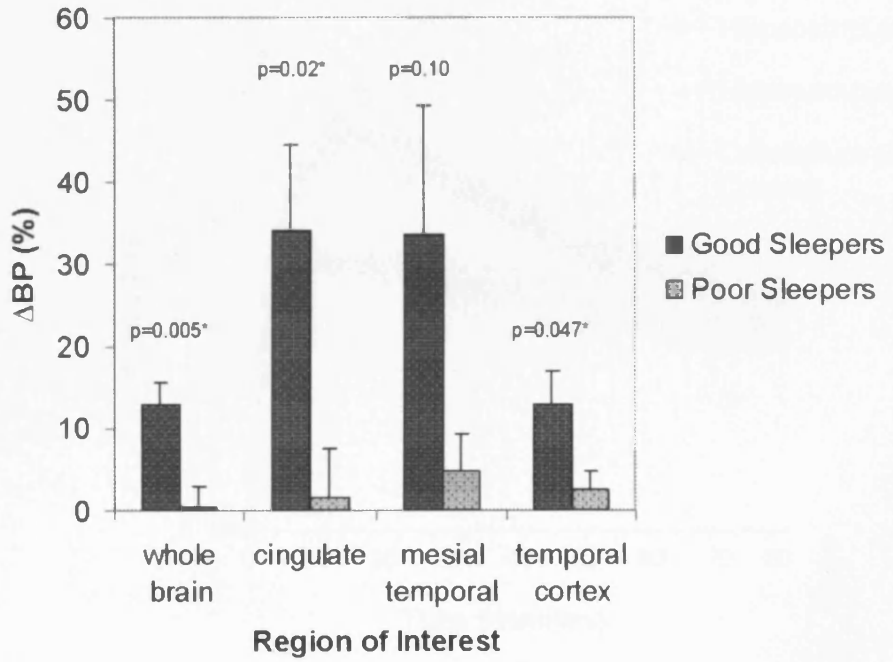


Figure 11. 1 *A comparison of mean ΔBP in 'Good sleepers' and 'Poor sleepers', showing significantly larger ΔBP values in 'Good sleepers'. Error bars are of the standard error of the mean.*

15) and for the sleep scan was 4.5 (range 0-13). Mean serum tryptophan levels were 60 (± 16) μM for the wake scan, and 57 (± 15)μM for the sleep scan. Stepwise regression showed no significant correlation between ΔBP and serum tryptophan levels, change in BAI and BDI scores, methylphenidate dose or ΔR_0 in the whole brain.

Part II: Rat β-microprobe study

Administration of high dose methylphenidate induced no displacement of [^{18}F]MPPF in 5 rats. Time-activity curves from the β-microprobe are shown in Figure 11.2; it can be seen that the time-activity curves of the methylphenidate treated rats and the control rats showed no difference in [^{18}F]MPPF binding following the methylphenidate bolus.

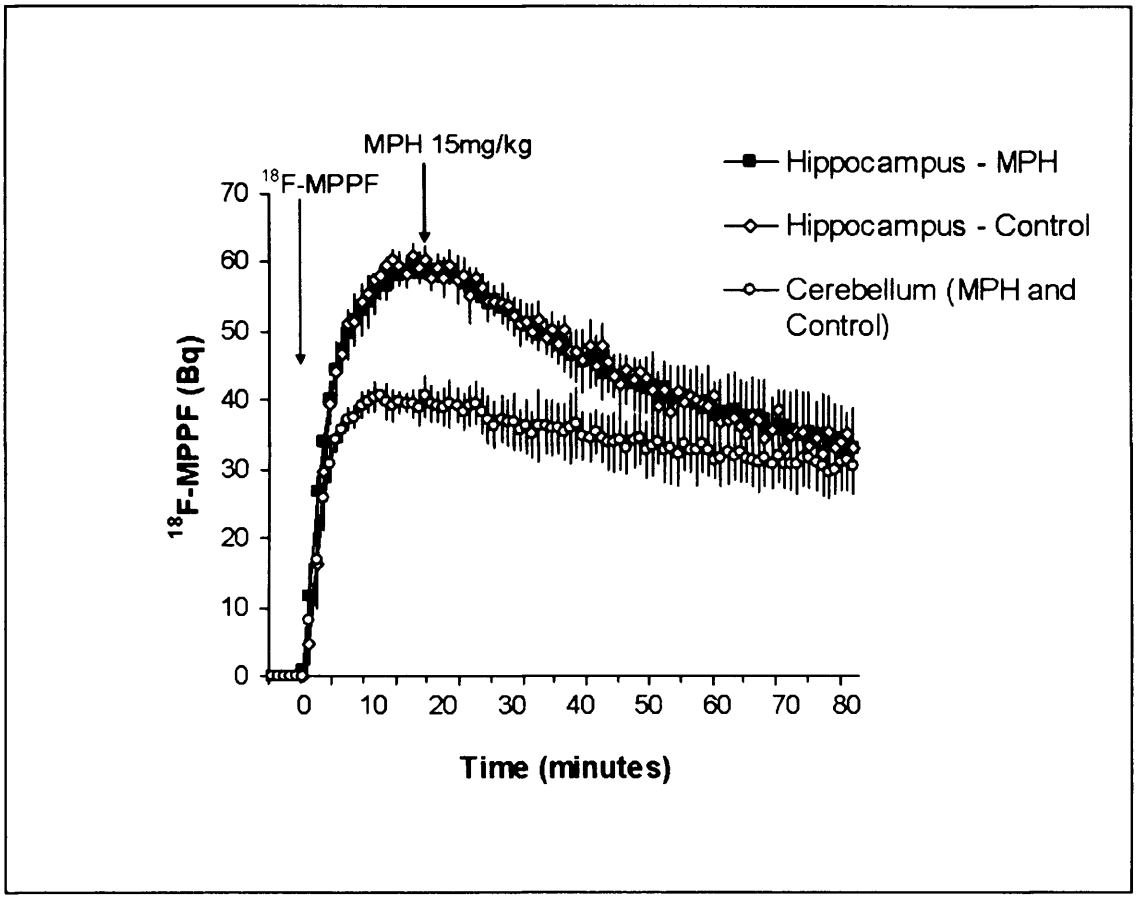


Figure 11. 2. *Time– activity curves measured by β-microprobes located in the hippocampus and cerebellum of rats following an intravenous injection of 2mCi [18F]MPPF. Time–activity curves from control rats and rats treated at 20 min with methylphenidate (MPH) are shown and are indistinguishable, demonstrating that methylphenidate injection has no effect on [18F]MPPF binding. Error bars are of the standard error of the mean.*

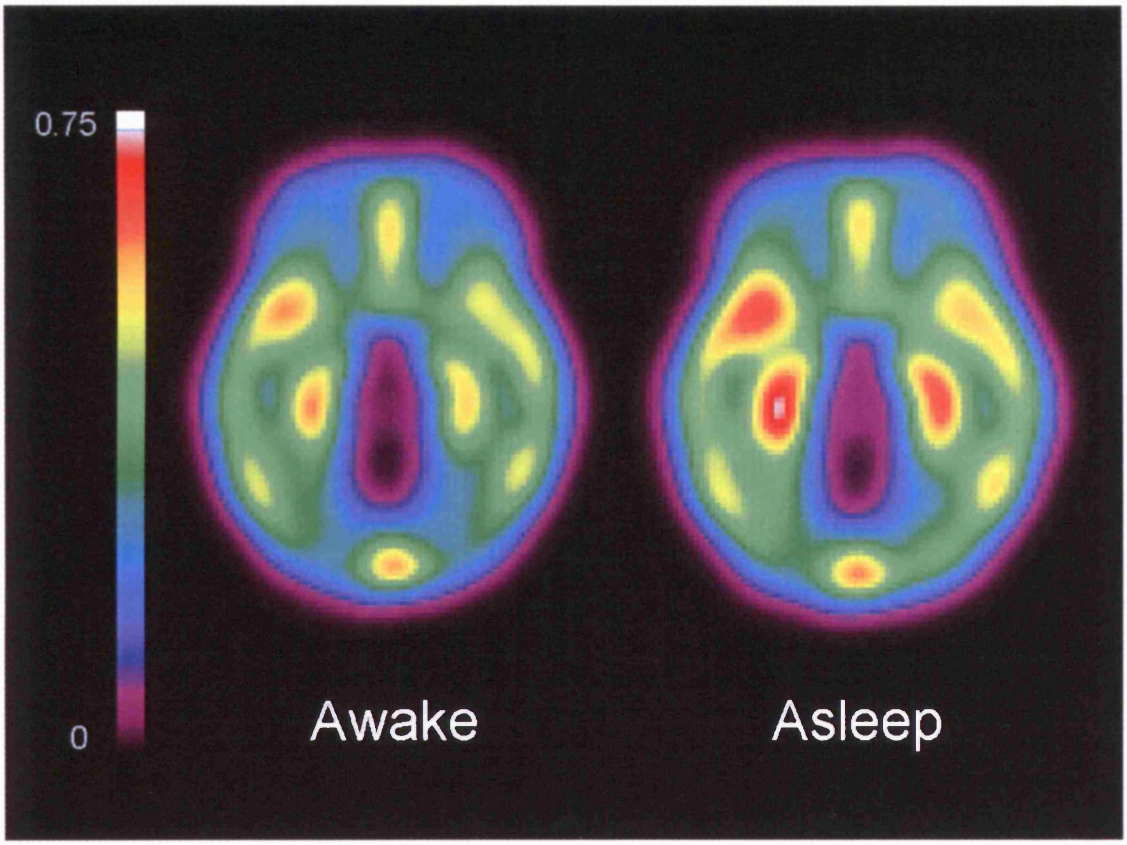


Figure 11. 3. *Parametric images of mean representative ^{18}F-MPPF Binding Potential (BP) in the group of 'Good sleepers' in wakefulness and sleep, spatially normalized to common stereotaxic coordinates. A widespread increase in BP is present in the sleep image, seen here in the mesial temporal and temporal cortical regions.*

Discussion

This study has demonstrated an increase in [^{18}F]MPPF binding in sleep, indicating increased $5HT_{1A}$ receptor availability in sleep compared to wakefulness. To my knowledge, this is the first time such changes have been demonstrated in humans.

Relationship to endogenous serotonin release.

[^{18}F]MPPF is a selective $5HT_{1A}$ receptor antagonist (Thielen and Frazer, 1995). It has an affinity for the $5HT_{1A}$ receptor (K_i=3.3nM) comparable to that of serotonin (K_i = 4.7nM) (Zhuang et al., 1994), and a number of studies in anaesthetized rats have indicated that [^{18}F]MPPF binding is sensitive to endogenous serotonin release (Zimmer et al., 2002; Rbah et al., 2003). These changes in [^{18}F]MPPF binding may simply reflect competitive inhibition of ligand binding by endogenous serotonin, although observations of the effect of endogenous ligand on dopamine D1 receptor binding have given rise to an alternative explanation based on receptor trafficking (Laruelle, 2000). In this model, the release of endogenous ligand results in receptor internalization and reduced radioligand binding (see Chapter 3, page 77-78 for further details).

This study is the first to examine changes in [^{18}F]MPPF binding with physiological changes in endogenous serotonin, in contrast to previous animal studies in which the pharmacological challenges used may have produced supraphysiological fluctuations. However, a previous attempt to influence serotonin release in humans using tryptophan depletion and supplementation did not alter [^{18}F]MPPF binding in humans (De Haes et al., 2002). It is likely that larger changes in serotonin release occur in sleep as observed in the present study than are achieved by manipulation of blood tryptophan concentration. The reduction in central serotonin concentration following tryptophan depletion is approximately 30% and occurs after 8-12 hours (Carpenter, 1998). Tryptophan infusions produce only minor and transient increases in central serotonin release (Ternaux, 1976; Hoebel, 1989).

Recently the same group was also unable to demonstrate changes in [^{18}F] MPPF binding in conscious monkeys, despite inducing supraphysiological increases in serotonin using fenfluramine (de Haes et al., 2006). The authors concluded that this result was due to the capacity of the $5HT_{1A}$ to exist in either a 'high affinity' or 'low affinity' state (Nenonene et al., 1994; Watson et al., 2000). As antagonists (including [^{18}F] MPPF) will bind equally to receptors in the low and high affinity states, whereas agonists (including endogenous serotonin) will preferentially bind to receptors in the high affinity state (Nenonene et al., 1994; Watson et al., 2000), [^{18}F] MPPF binding will only be altered by endogenous serotonin if sufficient receptors are in the high affinity state. It was suggested that changes in [^{18}F] MPPF binding are observed in anaesthetized rats, but not conscious monkeys, because a greater proportion of $5HT_{1A}$ receptors are in the high affinity state during anaesthesia than in wakefulness (de Haes et al., 2006). This concept is speculative, but may be relevant to the current findings. It is conceivable that the altered [^{18}F] MPPF binding observed in this study is not solely a reflection of endogenous serotonin release, but is also influenced by changes in the affinity state of $5HT_{1A}$ receptors. The current findings indicate that serotonin receptor availability changes through the sleep-wake cycle, but whether this is synonymous with serotonin release alone is yet to be fully clarified.

The involvement of serotonin in myriad neuropsychological functions such as cognition and emotion (Meneses, 1999), as well as neuropsychiatric conditions such as depression, schizophrenia and dementia (Sumiyoshi et al., 1996; Celada et al., 2004), has led to considerable interest in studying endogenous serotonin release. The wide range of applications would parallel the use of competitive displacement of [^{11}C] raclopride (Koepp et al., 1998) to measure dopamine fluxes induced by behavioral and pharmacological manipulations *in vivo*. Although established $5HT_{1A}$ ligands, such as WAY 100635, have not been shown to be sensitive to endogenous serotonin release (Maeda et al., 2001), [^{18}F] MPPF may prove to be a useful ligand for this purpose.

Methodological considerations.

Factors other than conscious state which may have affected the results of this study included the omission of methylphenidate prior to the sleep scan. However, this is unlikely to have been a significant effect. Firstly, there is evidence that methylphenidate blocks presynaptic dopamine uptake (Schenk, 2002), but has negligible effect on serotonergic neurotransmission (Kuczenski and Segal, 1997; Segal and Kuczenski, 1999). Secondly, no correlation between dose of methylphenidate and magnitude of change in [^{18}F]MPPF binding was observed in the current study; some of the largest changes in binding potential were seen in untreated subjects. Finally, the data from the β-microprobe study in which methylphenidate was administered at high doses (substantially higher than therapeutic doses in humans), demonstrated no change in [^{18}F]MPPF binding in methylphenidate-treated rats compared to controls (Figure 3). These data strongly suggest that the changes in [^{18}F]MPPF binding observed the current study were not influenced by methylphenidate. Other factors, including mood, circadian effects and dietary tryptophan, were carefully controlled for.

The K_1 ratio term (R_0) in the simplified reference tissue model used reflects relative tracer delivery between the tissue of interest and the cerebellar reference region (Lammertsma and Hume, 1996). There was no significant correlation between ΔR_0 and ΔBP making it unlikely that changes in BP were an artifact of altered tracer delivery. There was a small but statistically significant increase in R_0 in sleep compared to wakefulness in the cingulate, mesial temporal and temporal cortex regions of interest. This finding is consistent with previous studies of cerebral blood flow demonstrating greater reductions in blood flow in the cerebellum than in cortical regions during sleep (Sakai et al., 1980; Braun et al., 1997; Hofle et al., 1997). The magnitude of the cerebral blood flow changes observed previously cannot account for the large changes in BP observed in this study.

Subjects with narcolepsy-cataplexy were studied to increase the likelihood of sleep during the scans. This raises issues as to the generalisability of the findings to normal sleep. Narcolepsy is a neurological condition characterized by chronic

sleepiness and intrusions into wakefulness of REM sleep phenomena including hallucinations, cataplexy and sleep paralysis. Polysomnographic measures of sleep in this condition are qualitatively similar to normal sleep although REM latency is reduced (Broughton and Mamelak, 1980; Montplaisir and Godbout, 1986). There is now compelling evidence that narcolepsy results from the loss of hypocretin-producing neurons in the dorsolateral hypothalamus (Nishino et al., 2000; Mignot et al., 2003) and that fundamental changes in the serotonergic system are not directly responsible (see Chapter 2 page 49 for details). Secondary changes may lead to reductions in serotonergic inhibiton of REM-on neurons early in sleep (Brown et al., 2002; Liu et al., 2002). However, it seems likely that similar patterns of serotonin release occur in normal sleep, although this requires empirical confirmation. While functional neuroimaging studies of sleep in normal subjects have been accomplished with the aid of preceding sleep deprivation, these are more difficult to perform. Moreover, there is considerable evidence to suggest that sleep deprivation may have influences on serotonergic neurotransmission (Prevot et al., 1996; Gardner et al., 1997), although such influences have not been studied in humans and are not fully understood. In the absence of a practically achievable ideal methodology, the study of subjects with narcolepsy-cataplexy provides a workable means of obtaining sleep during the experimental procedure.

Serotonin and sleep.

A detailed understanding of the neurochemical changes in human sleep is essential for a full understanding the role of sleep in health and disease, and to develop effective treatments for sleep disorders. Serotonin has long been thought to play a key role in sleep on the basis of findings in animals (Jouvet, 1972). However, in light of the substantial interspecies variations that have been demonstrated in serotonergic function (Cragg et al., 1997; Antle et al., 2003), the extrapolation of such findings to human sleep may be misleading. In our study we have provided substantial evidence that serotonin receptor availability is increased in the human brain during sleep, a finding consistent with existing animal data. We also found that changes in binding during the sleep-wake cycle were widespread throughout the brain. While the raphe nuclei have widespread efferent connections, different target regions in the central nervous system are innervated by anatomically distinct

subpopulations of raphe neurons; these may be differentially activated in some behavioral states (Fornal 1996). Our findings, however, suggest that this does not occur during sleep when a global change in serotonin receptor availability is observed.

Conclusion

In conclusion, this study demonstrated widespread changes in [^{18}F]MPPF binding consistent with increased serotonin receptor availability during sleep in the brains of subjects with narcolepsy. These findings confirm a role for serotonin in the modulation of human sleep. Moreover they suggest that [^{18}F]MPPF PET may provide a valuable tool for the further investigation of serotonergic neurotransmission.

CHAPTER 12

SLEEP DISORDER OR SEIZURE? DIAGNOSING BUMPS IN THE NIGHT

Introduction

The diagnosis of abnormal paroxysmal motor events in sleep presents a particular challenge for the clinician. On the one hand, they may be parasomnias, benign non-epileptic sleep disorders defined as 'unpleasant or undesirable behavioural or experiential phenomena that occur predominantly or exclusively during the sleep period' (ASDA, 2005). On the other hand, they may be epileptic seizures, requiring investigation and treatment. In many cases, distinguishing seizures and parasomnias by means of the clinical history is relatively straightforward (Mahowald and Ettinger, 1990). However, frontal lobe epilepsy can be difficult to accurately diagnose. Seizures in frontal lobe epilepsy have a predilection for sleep and, in many patients, are entirely restricted to sleep. Nocturnal Frontal Lobe Epilepsy (NFLE) occurs sporadically or as an inherited form with an established genetic basis (Autosomal Dominant Nocturnal Frontal Lobe Epilepsy, ADNFLE) (Scheffer et al., 1995). Mutations in the genes encoding the α4 and β2 subunits of the neuronal nicotinic acetylcholine receptor (*CHRNA4* and *CHRNB2*), and more recently in the gene coding for the α2 subunit, have been associated with ADNFLE (Steinlein et al., 1995; De Fusco et al., 2000; Phillips et al., 2001), although such mutations are only identified in a minority of families with this condition (Combi et al., 2004). Seizures in NFLE may have bizarre clinical features, with vocalisation, complex automatisms and ambulation; investigation with electroencephalography and magnetic resonance imaging often shows no abnormality (Provini et al., 1999). These characteristics result in frequent misdiagnosis, with the events often being labelled as pseudoseizures or parasomnias, and some cases previously being designated as 'paroxysmal nocturnal dystonia' (Scheffer et al., 1994). Such misdiagnoses are clearly to the detriment of the patient, who may be denied appropriate treatment.

Conversely, some parasomnias are violent or dramatic, and may be confused with NFLE. While typical parasomnias are usually recognized as benign events, some individuals, in whom events are severe or frequent, come to medical attention. Such subjects present a diagnostic dilemma, and are sometimes incorrectly diagnosed with, and treated for, epilepsy. Parasomnias may also cause difficulties in the research setting, particularly in genetic studies of ADNFLE. Diagnostic accuracy is essential in genetic research, as linkage and molecular genetic studies rely upon precise phenotyping. Parasomnias, potential phenocopies of NFLE, are common, occurring in up to 15% of the general population (see chapter 10, page 171 for further discussion), and they may therefore appear in large ADNFLE kindreds. Incorrect inclusion of phenocopies, or exclusion of actual cases due to misdiagnosis, may result in the failure of linkage or the generation of spurious results.

A number of historical features have been described which may distinguish NFLE from parasomnias (Provini et al., 1999; Zucconi and Ferini-Strambi, 2000), but the value of these features has not been systematically assessed or directly compared between the conditions. Moreover, although rigorous scientific studies of NFLE have been undertaken, most clinical descriptions of parasomnias are based on smallsamples or clinical anecdote. As a result, most authorities recommend video-EEG or video EEG-polysomnography (Zucconi and Ferini-Strambi, 2000) for the diagnosis of paroxysmal nocturnal events. These investigations involve monitoring the patient in sleep through neurophysiological, video, and sometimes cardio-respiratory modalities, and recording their nocturnal events. They are expensive and inconvenient investigations requiring admission to hospital, and are only practical if the nocturnal events are happening on a frequent, preferably nightly, basis. In those patients with less frequent events it will often not be possible to capture an event during a monitoring period, in which case the investigation will not usually clarify the diagnosis. From a practical perspective, access to video-EEG and polysomnography monitoring services varies widely in different regions, and for many patients these investigations are not readily available. In genetic studies, affected individuals (either with ADNFLE or parasomnias) may no longer be experiencing events, as both conditions often remit in adulthood. In such situations, phenotyping relies entirely on the history.

In many cases, therefore, the effective standard for diagnosis is the expert clinical interview. However, at present the reliability of the history in discriminating between NFLE and parasomnias is unclear. Many individual components (such as screaming, standing, and complex behaviours) have been reported in both conditions (see Chapter 7, pages 133-4 and Chapter 10, pages 185-90, for additional discussion) and the relative discriminatory value of such features is unclear. There is, therefore, a need to address this issue, and provide an evidence-based diagnostic approach for situations in which video-EEG and polysomnography are impractical or unhelpful.

Aims and Hypotheses

Aims:-

To assess the usefulness of historical features in distinguishing nocturnal frontal lobe epilepsy from parasomnias, by:

(i) the development and validation of a clinical scale, the Frontal Lobe Epilepsy and Parasomnias (FLEP) Scale, based on reported differences between nocturnal frontal lobe seizures and parasomnias.

(ii) a direct statistical comparison of historical features in a population of individuals with established diagnoses of parasomnias or NFLE.

Hypotheses:

(i) The FLEP scale is a reliable instrument for distinguishing NFLE from parasomnias when compared with the clinical current 'gold standard' diagnostic evaluation (i.e. expert interview and, when necessary, recording of events using video EEG monitoring)

(ii) Clear differences are identifiable in the historical features of NFLE and parasomnias on statistical analysis

Methods

Scale Development

The FLEP scale (Figure 12.1) was developed, following review of the literature, by an expert panel. This panel comprised Professor Samuel Berkovic (neurologist/ epileptologist), Professor Ingrid Scheffer (paediatric neurologist/ epileptologist), Dr Murray Johns (sleep physician), Dr Carla Marini (neurologist) and the author. The scale consists of a series of specific questions based on the clinical features of NFLE and parasomnias. Particular consideration was given to the NREM arousal parasomnias such as sleep walking and night terrors, as these conditions are most commonly confused with NFLE (Provini et al., 1999; Zucconi and Ferini-Strambi, 2000), but the scale was designed to be broadly applicable. Questions were designed to address those features which, according to the medical literature and in the experience of the clinicians involved, are useful in discriminating between the conditions (see Chapter 10, pages 185-190 for detailed literature review). A choice of possible responses was assigned to each question, each with a score. Responses favouring epilepsy (such as events of brief duration, occurring multiple times per night) scored positively, and those favouring parasomnias (such as coherent speech without recall) scored negatively. Those features considered to be particularly strong indicators of either condition were given greater weighting, based on the findings of a pilot study of 18 case histories; these 18 cases were not recruited into the formal validation study. The study was designed such that the total score, calculated by summing the individual scores on completion of the scale, should predict the correct diagnosis - an overall positive score should indicate epilepsy, and a zero or negative score should indicate parasomnias.

In addition to the clinical scale, a semistructured interview questionnaire was designed to form the basis of the telephone interview (see Appendix A for details). This included all the clinical features alluded to in the FLEP scale, but also included other features which could potentially be observed at different frequencies in parasomnias and NFLE.

Clinical Feature	Response	Score
Age at onset:- At what age did the patient have their first clinical event?	Under 55 years of age 55 years or older	0 -1
Duration:- What is the duration of a typical event?	Less than 2 minutes 2-10 minutes Longer than 10 minutes	+1 0 -2
Clustering:- What is the typical number of events to occur in a single night?	One or two events only 3 to 5 events More than 5 events	0 +1 +2
Timing:- At what time of night do the events most commonly occur?	Within 30 minutes of sleep onset Other times (including if no clear pattern identified)	+1 0
Semiology:- Are the events associated with a definite aura?	Yes No	+2 0
Does the patient ever wander outside the bedroom during the events?	Yes No (or uncertain)	-2 0
Does the patient perform complex, directed behaviours (eg picking up objects, dressing) during events?	Yes No (or uncertain)	-2 0
Is there a clear history of prominent dystonic posturing, tonic limb extension or cramping during events?	Yes No (or uncertain)	+1 0
Stereotypy:- Are the events highly stereotyped or variable in nature?	Highly stereotyped Some variability/ uncertain Highly variable	+1 0 -1
Recall:- Does the patient recall the events?	Yes, lucid recall No, or vague recollection only	+1 0
Vocalisation:- Does the patient speak during the events and, if so, is there subsequent recollection of this speech?	No Yes, sounds only or single words Yes, coherent speech *with incomplete or no recall* Yes, coherent speech *with recall*	0 0 -2 +2
	Total Score	

Figure 12. 1. *The Frontal Lobe Epilepsy and Parasomnias (FLEP) scale.*

Scale Validation and Statistical Analysis

Inclusion and exclusion criteria. The study population comprised patients who had been referred to a sleep physician or neurologist with a history of nocturnal events of uncertain cause. Individuals with NFLE were eligible for the study if they had a history consistent with NFLE and at least one of the following: video-EEG monitoring with clinical or electrographic evidence of nocturnal frontal lobe seizures; or a genetic mutation consistent with Autosomal Dominant Nocturnal Frontal Lobe Epilepsy (ADNFLE). In families with ADNFLE, no more than two family members from the same kindred were recruited. Patients with parasomnias were recruited in two subgroups. The first group consisted of subjects who were referred to a sleep clinic for diagnosis of their nocturnal events, but in whom a definite diagnosis of 'typical' parasomnia was made by the specialist on the basis of the history and without recourse to video EEG monitoring. This specialist, Dr Margot Davey, was an independent sleep paediatrician with extensive experience in the diagnosis and management of parasomnias, and was not involved in the scale validation process. The second group comprised cases in which there was diagnostic uncertainty on the basis of the history alone and in which the diagnosis was established by video EEG or video polysomnography (PSG) monitoring. These cases were designated 'atypical' parasomnias.

Recruitment. Patients with nocturnal events were recruited from four centres in Melbourne, Australia (Austin Health, Royal Children's Hospital, Monash Medical Centre and Epworth Hospital). Subjects with NFLE and 'atypical' parasomnias (confirmed by video EEG/PSG monitoring) were recruited retrospectively from a review of existing medical databases and records covering a 10 year period. All patients with confirmed diagnoses who could still be contacted were approached regarding participation as well as all new cases identified during admission for investigation over a two year period. Subjects with 'typical' parasomnias were recruited as a consecutive case series presenting to a paediatric sleep clinic over a two year period. All subjects gave their written informed consent to the study protocol, which was approved by the medical ethics committees of the Austin, Royal Children's, Monash and Epworth Hospitals.

Scale administration. Semi-structured interviews (Appendix A) were conducted twice for each subject by different researchers on separate occasions. The two interviews were at least four weeks apart. One interviewer was a research assistant experienced in taking epilepsy histories, but without medical training. The other was the author, a medical practitioner with experience of the diagnosis and treatment of sleep disorders and epilepsy. The researchers were blinded to the patients' identities and diagnoses, as well as to each other's interviews. During the interviews, clinical information was obtained from the patient and a witness (usually a partner, relative or parent). Participants were reminded at recruitment and at the start of each interview not to discuss the nature of any investigations, treatment or the diagnosis they had received.

Statistical Analysis – validation study. For the statistical analysis, the FLEP scale was treated as a diagnostic test for NFLE, with a total score of +1 or greater indicating a diagnosis of epilepsy, and a score of zero or less indicating parasomnias. Sensitivity, specificity and positive and negative predictive values were calculated, with 95% confidence intervals. Inter-rater agreement for the diagnosis was assessed using Cohen's Kappa (Cohen, 1960).

Statistical Analysis – all historical features. In addition to the validation study of the FLEP scale, the discriminatory value of each individual historical feature identified in the semistructured interview (as recorded by the author) was examined between NFLE and NREM arousal parasomnias. Fisher's exact test was applied for categorical variables, and the Mann-Whitney U test was used for continuous variables. All statistical tests were performed using SPSS 14.0 software. As recommended by several authorities (Rothman, 1986; Perneger, 1998), no statistical adjustments were made for multiple comparisons, but the dataset is presented in its entirety with the results of all comparisons displayed. To identify the most important individual clinical features in predicting a diagnosis of NFLE or parasomnias, multivariate analysis using binary logistic regression (forward stepwise selection method) was also performed using Statistical Package for Social Sciences (SPSS) 14.0 software.

Results

Subjects

The study was undertaken between the 1st June 2003 and 1st June 2005. 84 subjects who met the entry criteria for the study were identified. Twenty-two subjects were not contactable or declined to participate in the study, leaving a total of 31 participants (15 males) with NFLE, 11 (8 males) with 'atypical' parasomnias and 20 (12 males) with 'typical' parasomnias. All patients with 'atypical' parasomnias and NFLE had undergone diagnostic video EEG monitoring. The specific diagnoses for the participants were: 8 ADNFLE, 23 sporadic NFLE, 29 NREM arousal disorders (confusional arousals, sleepwalking or sleep terrors) and 2 REM sleep behaviour disorder (RBD). In the NFLE group, the median age of subjects in the study was 18 years (range 12 – 77 years), and the median age of symptom onset was 7 years (range 6 months – 27 years); in the NREM arousal parasomnia group the median age of subjects was 9.5 years (range 2 – 53 years), and the median age of symptom onset was 4 years (range 6 months – 16 years); and in the RBD group the median age in the study was 69.1 years (range 62 – 77 years) with a median age at onset of 64.0 years (range 55 – 73 years).

Validation Study (FLEP scale)

There was almost perfect inter-rater agreement in diagnosis based on the FLEP scale, with a Kappa statistic of 0.97.

The median FLEP score for the NFLE group was +5 (range +1 to +11). The median score for the complete parasomnia group was -4 (range -12 to +3); for the 'typical' parasomnias it was -4 (range -9 to -1) and for the 'atypical' parasomnias -4 (range -12 to +3). The distribution of scores according to diagnosis is given in Figure 12.2.

For interviewer 1 (non-medically trained), sensitivity was 1.00 (95% CI 0.86 – 1.00), specificity was 0.90 (95% CI 0.73 - 0.97), positive predictive value was 0.91 (95% CI 0.75 - 0.97), and negative predictive value was 1.00 (95% CI 0.85 – 1.00). For interviewer 2 (medically trained), sensitivity was 1.00 (95% CI 0.86 –

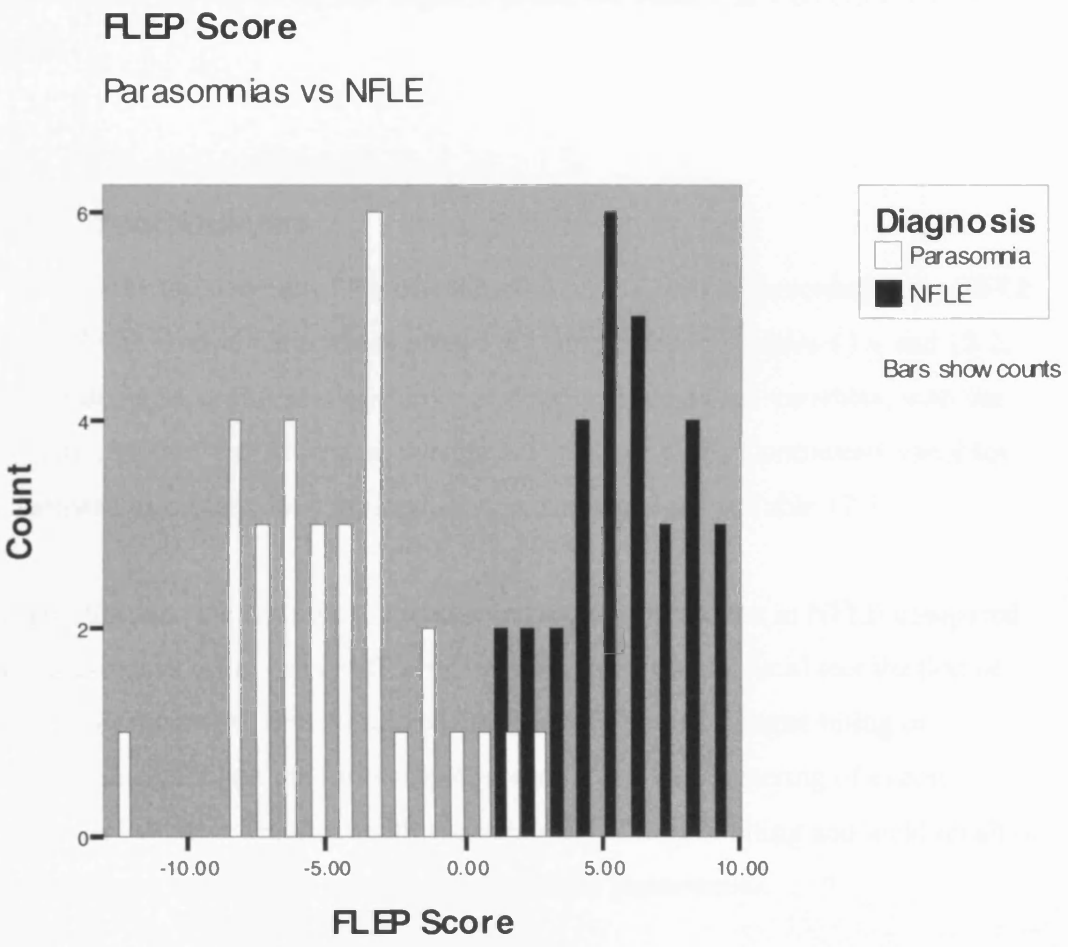


Figure 12. 2. *Frequencies of FLEP scores generated by the non-medically trained interviewer, colour coded according to actual diagnosis. Of the 62 patients interviewed, a total of 3 were incorrectly diagnosed using the scale; these were all parasomnias who generated low positive scores. The graph generated by the medically trained interviewer is very similar, but with only 2 misdiagnoses.*

1.00), specificity was 0.93 (95% CI 0.79 - 0.98), positive predictive value was 0.94 (95% CI 0.78 - 0.98) and negative predictive value was 1.00 (95% CI 0.85 – 1.00).

Statistical Analysis

The relative frequencies of the individual historical features recorded in the NFLE and NREM arousal parasomnia groups are summarised in Tables 12.1 and 12.2, and ordered according to statistical significance. Categorical variables, with the results of Fisher's exact test, are displayed on Table 12.1. Continuous variables, evaluated using the Mann Whitney U test, are displayed in Table 12.2.

From this data, the features reported significantly more often in NFLE compared to parasomnias were aura, stiffening or abnormal postures, lucid recollection of events, events in the first 30 minutes of the sleep period, tongue biting or incontinence, fatigue the following day, stereotypy and clustering of events. However, all these features (with the exception of tongue biting and lucid recall of events) were also seen in some individuals with parasomnias.

The features reported significantly more frequently in parasomnias were coherent speech, wandering outside the bedroom, complex directed behaviours and timing of events in the first third of sleep (but after the first 30 minutes). Again, however, all these features were seen in a proportion of individuals in NFLE; none occurred exclusively in parasomnias.

Several features were frequently reported in both conditions. In particular, clear trigger factors (usually stress, sleep deprivation or intercurrent illness), shouting or screaming, and a family history of nocturnal events were commonly described in both. A vague recollection of episodes was less common but reported at similar frequencies in both disorders.

Historical feature	%age of parasomnias (28 cases)	%age of NFLE (31 cases)	p value
Aura	4%	45%	<0.001
Stiffening/ abnormal postures	18%	77%	<0.001
Lucid recall of episodes	0%	52%	<0.001
Events in first 30 minutes of sleep	7%	55%	<0.001
Fatigued next day	32%	81%	<0.001
Tongue biting	0%	35%	<0.001
Stereotypy	57%	90%	0.006
Clustering	21%	58%	0.007
Incontinence	4%	29%	0.013
Anytime/ no pattern	11%	26%	0.11
Triggers to events (stress/ illness etc)	61%	81%	0.15
Recall of coherent speech	4%	16%	0.20
Psychiatric or behavioural problems	11%	16%	0.71
Developmental delay	7%	11%	1.00
Vague recollection of episodes	25%	19%	0.76
Family history of nocturnal events	57%	42%	0.30
Shouting/ screaming	75%	58%	0.27
Coherent speech	71%	26%	0.001
Complex directed behaviours	45%	7%	0.001
Wandering outside the bedroom	75	26	<0.001
Events in first 1/3 of night (not first 30 minutes)	82%	19%	<0.001

Table 12. 1. *Categorical variables recorded from the semistructured interview of subjects with parasomnias or NFLE, and ranked according to the statistical significance of the difference between the groups. Statistical comparison is made using Fisher's exact test. Shaded variables are those which reach statistical significance (threshold $p \leq 0.05$).*

Historical feature	Mean for parasomnias (28 cases)	Mean for NFLE (31 cases)	t statistic	p value
Max number of events per 'attack night'	2.5	15	5.2	<0.001
Typical number of events per 'event night'	1.25	6	4.7	<0.001
Maximum duration witnessed (minutes)	14.6	1.7	-5.3	<0.001
Typical duration witnessed (minutes)	7.5	0.9	-4.9	<0.001
Age at onset (years)	4.9	8.1	2.48	0.02
Typical number of 'attack nights' per month	11.8	16.5	1.83	0.08

Table 12. 2. *Continous variables recorded from the semistructured interview of subjects with parasomnias or NFLE, and ranked according to the statistical significance of the difference between the groups. Statistical comparison is made using the Mann-Whitney U test. Shaded variables are those which reach statistical significance (threshold $p \leq 0.05$).*

Clinical Feature	B	Wald χ value	p value	odds ratio	Odds ratio 95% CI	
					Lower	Upper
First 1/3 of sleep (not first 30 minutes)	-3.92	10.3	0.001	0.02	0.006	0.201
Aura	3.36	7.6	0.006	27.5	2.6	291.5
Wandering outside the bedroom	-3.13	6.8	0.009	0.04	0.004	0.464

Table 12. 3. *Results of the multivariate analysis, showing the significant variables identified through stepwise logistic regression ranked according to the statistical significance. The table shows the logistic regression coefficient (B), odds ratio and Wald χ^2 value for each of the predictor variables.*

Table 12.3 shows the logistic regression coefficient, Wald test and odds ratio for the significant variables included in the model generated by the stepwise logistic regression analysis. The presence of an aura was the most significant positive indicator of epilepsy; wandering outside the bedroom and a typical onset in the first third of the sleep period (but after the first half hour) were significant predictors of parasomnias. Other variables, although significant in the univariate analysis, did not reach statistical significance in the multivariate analysis.

The odds ratios from the logistic regression analysis indicate that the odds of a history of aura are 27.5 times greater in the NFLE group than parasomnias, the odds of a history of wandering outside the bedroom are 25 times greater in parasomnias than epilepsy, and the odds of a typical onset in the first third of sleep (but after the first 30 minutes) in parasomnias are 50 times those in NFLE. However, the confidence intervals for these values are very wide (Table 12.3).

A test of the model arising from the stepwise logistic regression analysis, using the three statistically significant variables (aura, wandering out of the bedroom and onset in the first third of sleep), was statistically significant at ($p<0.001$) when compared to one with intercept only. With this data, the model has an overall diagnostic success rate of 93% (NFLE is diagnosed with a sensitivity of .90 [95% CI 0.73-0.97] and a specificity of 0.96 [95% CI 0.79-0.99]).

Discussion

Principal findings

Paroxysmal events in sleep can pose a significant diagnostic challenge in both clinical practice and genetic research. While a number of conditions are associated with motor activity in sleep, particular confusion can arise when trying to differentiate between NREM arousal parasomnias and NFLE. This confusion arises through the similarities in the clinical presentation of these conditions, and the fact that in both conditions investigation with MRI and interictal EEG is often normal (Zucconi et al., 1997; Provini et al., 1999). While potential differences in the historical features of these conditions have previously been reported (Provini et al., 1999; Zucconi and Ferini-Strambi, 2000), their usefulness has not previously been systematically examined. Although the studies of NFLE which led to the identification of these features are thorough, the comparisons themselves are largely anecdotal, and contain limited direct study of parasomnias. Reported differences are usually couched in terms of 'red flags'; in other words, as features which should raise the clinical suspicion of epilepsy as a prelude to video EEG monitoring. This investigation is currently considered essential to confirm a diagnosis of NFLE or troublesome parasomnias. (Provini et al., 1999; Zucconi and Ferini-Strambi, 2000). In this study, however, by examining a sample of individuals referred to tertiary centres with nocturnal events, we have confirmed clear differences in the presenting features of these conditions. More significantly, we have also shown that historical features are usually sufficient to reliably make a diagnosis of NFLE or parasomnias without confirmatory video EEG monitoring, even in atypical cases. If a careful history is taken, and weighted appropriately, the correct diagnosis will be reached in almost 95% of cases.

The FLEP scale has been shown to be a valid and reliable instrument for facilitating the diagnostic process and may, therefore, be a useful tool particularly for clinicians with limited direct experience with nocturnal frontal lobe epilepsy. The sensitivity of 1 and specificity of 0.9 is good for a test of this kind, and a Cohen's Kappa of 0.97 indicates almost perfect inter-rater reliability. While both

individuals conducting the interviews had some experience in taking epilepsy histories, the fact that the scores of the physician and the research assistant (who is not medically trained) were very similar suggests that specialist epileptological or sleep training is not required to reliably use the scale.

The examination of individual clinical features was largely concordant with existing reported differences, with a couple of notable exceptions. Stereotypy, which is widely cited as strongly suggestive of NFLE (Provini et al., 1999; Zucconi and Ferini-Strambi, 2000), was reported in over half the parasomnia group suggesting that this feature is not very useful from a diagnostic perspective. Trigger factors (such as fatigue or stress) have previously been reported as more common in parasomnias than NFLE (Provini et al., 1999), this was not born out in our findings. Other previously reported features, however (such as increased frequency, brief duration, presence of aura and clustering in NFLE, and onset in the first third of sleep and complex directed behaviour in parasomnias), were reported at different rates in the NFLE and parasomnias.

It is remarkable, however, that very few features were reported exclusively in one condition. Tongue biting was never reported in parasomnias, but was also not particularly common in NFLE (although 35% of the NFLE reported tongue biting on at least one occasion, it was usually an infrequent manifestation of their seizures). Lucid recall in at least a proportion of events was a relatively common feature in the NFLE group, and was never reported in parasomnias (although vague recall was common in both groups). Apart from these two features, however, all the others were reported by subjects in both groups, albeit at different frequencies. This finding underlines the diagnostic difficulty facing clinicians in this situation – no individual clinical feature can be claimed to be a truly reliable indicator of either condition.

The result of the logistic regression analysis indicates that three features have the greatest predictive value in this situation. The single most important discriminatory variable favouring a diagnosis of epilepsy is aura, which was

present in almost half the NFLE series; occurrence in the first third of sleep (but not in the first half hour), and wandering out of the bedroom during some or all events, were both strongly predictive of parasomnias. The odds ratio for each of the three significant variables in the logistic regression analysis was very large, and possibly greater than might be expected. However, the very wide confidence intervals indicate that precision of these values is quite low. These confidence intervals are likely to be primarily a result of the sample size, which is relatively small for a multivariate analysis of this type, but there is also some collinearity between the variables examined. Thus while it can be stated with confidence that aura, wandering out of the bedroom, and occurrence in the first third of the sleep period (but after the first 30 minutes) are significant predictor variables in the diagnosis of NFLE or parasomnias, the precise magnitude of their predictive value is less clear. Other features, such as lucid recall of events and stiffening or posturing during episodes, while highly significant in the univariate analysis, did not significantly contribute to the accuracy of the multivariate model.

Overall, our data indicates that when the features of the history are taken in combination and weighted appropriately, a correct diagnosis will usually be made. This is useful, as it enables greater diagnostic confidence in situations when video EEG monitoring is unhelpful or not feasible.

Methodological Considerations

The main weakness of the study is the retrospective nature of recruitment for the monitored group of patients. These factors reflect the fact that nocturnal frontal lobe epilepsy is not common, and parasomnias, although reported in around 15% of the pediatric population (Agargun et al., 2004), are usually mild and do not require tertiary referral for diagnosis and management. In the group of severely affected patients, recording events during video EEG monitoring may still be difficult or impossible due to the unpredictable nature of the attacks. In view of the relatively small numbers of patients with confirmed video monitoring findings per year, it was not practical to administer the FLEP scale prospectively (i.e. before the diagnosis was confirmed by video monitoring).

A further potential criticism relates to the absence of confirmatory video EEG monitoring in the consecutive series of 'typical' parasomnias. The NREM arousal parasomnias (which cause most diagnostic confusion with respect to NFLE) are benign, quasiphysiological disorders which are notoriously difficult to capture on video EEG monitoring. Their occurrence is markedly influenced by sleeping environment, a finding that has been described in previous studies (Gastaut, 1965; Jacobson et al., 1965; Joncas et al., 2002), and often emerges in individual case histories. Thus, although from a scientific perspective such supportive data would be desirable, in reality obtaining it is impractical. If a secure diagnosis of parasomnias has been made by an expert on the basis of the history it is rarely justified, clinically or economically, to admit a child for prolonged monitoring, particularly as the investigation will often be fruitless.

It could, then, be argued that only the 'atypical' parasomnia group with confirmatory video EEG monitoring should have been included in the study, in order to make the diagnostic criteria as robust as possible. However, to have used such a methodology would have potentially distorted the findings; only patients with unusual and frequent parasomnias, in which there had been a very high suspicion of epilepsy, would have been included. While it was clearly vital to include such cases, as they are the most difficult to diagnose, it was also important to address the full clinical spectrum of parasomnias. We therefore included subjects in the 'typical' parasomnia group without video EEG data, but in the 'atypical' group (in whom the diagnosis was regarded as uncertain), video EEG monitoring confirmation of the diagnosis was mandatory. It is worth reiterating at this point that all subjects in the NFLE group (in addition to the 'atypical' parasomnia group) had been fully investigated, with confirmatory video EEG monitoring in all cases.

Use of the scale

Using the clinical features we have identified in the FLEP scale, an accurate assessment of the likelihood of epilepsy may be made at the initial consultation, even when the clinician has limited experience with these conditions. Appropriate

reassurance and management strategies may be given to those individuals with parasomnias, avoiding the need for specialist referrals and unnecessary anxiety and expense. Likewise, prompt investigation and management will be possible in those individuals with epilepsy. In ADNFLE genetic linkage studies, the scale may be used as a guide to the inclusion or exclusion of uncertain cases in whom video EEG monitoring is not possible.

From a practical perspective, there was a small degree of overlap in the FLEP scores for the two groups. We would conclude that, on the basis of this study, any patient with a score of zero or less is very unlikely to have epilepsy, and any score of greater than +3 is very likely to have epilepsy. In those with a score of +1 to +3, there is a relatively high chance of epilepsy, but further investigation would be desirable in these individuals; however, in our sample such subjects made up less than 20% of the total group.

While the reality of this difficult clinical problem is that some patients will always need confirmatory video EEG monitoring, an increased understanding of important discriminators in the history may reduce this need, as well as increasing diagnostic confidence in situations when the recording of events is not possible.

CHAPTER 13

THE NREM AROUSAL PARASOMNIAS: ANALYSIS OF ELECTROCLINICAL FEATURES AND COMPARISON WITH NOCTURNAL FRONTAL LOBE EPILEPSY

Introduction.

Parasomnias are divided on the basis of phenomenology into three subgroups: disorders of arousal from NREM sleep, parasomnias usually associated with REM sleep, and others (ASDA, 2005). The NREM arousal disorders are characterised by paroxysmal behaviours without conscious awareness, usually arising from stage 3 or 4 NREM sleep, and have a broad spectrum of clinical manifestations. In practice they are subdivided into three main forms, although common underlying mechanisms are believed to be responsible. *Confusional arousals* are associated with little motor or autonomic involvement; *somnambulism* (sleepwalking), is associated with motor activity but little autonomic involvement; and *sleep terrors (pavor nocturnus)*, involve prominent autonomic involvement accompanied by a variable degree of motor activity (Mahowald, 2002; ASDA, 2005). While the diagnosis of these conditions is often straightforward, some individuals present with frequent, severe or unusual episodes which raise the suspicion of epilepsy. Of particular concern is nocturnal frontal lobe epilepsy (NFLE), which also presents with varied and sometimes bizarre motor, vocal and behavioural manifestations from sleep (Montagna, 1992; Provini et al., 1999; Provini et al., 2000). As demonstrated in Chapter 12, distinguishing between parasomnias and NFLE on historical grounds is often possible but can sometimes be difficult. Challenging cases usually require the recording of events with video EEG monitoring; however, the situation is complicated by the fact that interictal and ictal EEG are frequently unremarkable or non-diagnostic in both parasomnias and NFLE (Provini et al., 1999; Zucconi and Ferini-Strambi, 2000), and the diagnosis is therefore often based primarily on ictal characteristics of the events as recorded on video. The semiology of frontal lobe seizures, and those occurring in NFLE in particular, have been established over the last 20 years (Williamson et al., 1985; Waterman et al., 1987; Salanova et al., 1995; Provini et al., 1999).

However, the ictal semiology of the NREM arousal parasomnias has not been studied in detail. Initial neurophysiological studies of the parasomnias contained general descriptions of event types, but were conducted in the pre video EEG monitoring era, and also predated the recognition of NFLE (Gastaut, 1965; Jacobson et al., 1965; Broughton, 1968). Subsequent reports of parasomnias contain very limited semiological information (Kavey et al., 1990; Zucconi and Ferini-Strambi, 2000), and few centres report direct experience of them. Therefore, although the broad behavioural characteristics of parasomnias are widely accepted, surprisingly little is known regarding the details of their ictal manifestations.

As a result of the paucity of information regarding parasomnias, distinguishing them from NFLE on video EEG monitoring may be difficult. In practice it is often a 'negative' process, based upon the absence of clear features of epilepsy, rather than on the identification of 'positive' features of parasomnias. Diagnostic uncertainty may remain even after events have been recorded. Moreover, although EEG findings in parasomnias are usually unhelpful, in some cases they may be misleading. Incidental interictal epileptiform discharges such as centrotemporal spikes, and normal arousal patterns such as rhythmic frontal rhythmic theta and delta activity may lead the clinician into towards an erroneous diagnosis of epilepsy.

In order to improve diagnostic certainty, more detailed descriptions of parasomnias are required. In this study a video EEG monitoring series of NREM arousal parasomnias was compiled to address this issue and provide an evidence-based approach to diagnosis.

Aims

The aims of this study were firstly to accurately describe the semiological and electrographic features of NREM arousal parasomnias; and secondly, to directly compare these features with those of NFLE.

Hypotheses

(i) Parasomnias have distinct, identifiable, semiological features and behaviour patterns.

(ii) Parasomnias and NFLE have different clinical presentations, identifiable through statistical analysis of elemental clinical features.

Methods.

Subjects

Parasomnia cases were recruited from three epilepsy monitoring centres (National Hospital for Neurology and Neurosurgery, Queen Square, London; Austin Hospital, Melbourne, Australia; and the Royal Children's Hospital, Melbourne, Australia); NFLE cases were from the Austin Hospital, Melbourne. In both groups the diagnosis was made on the basis of historical, imaging and EEG findings. Detailed histories were obtained through a review of clinical records and direct interviews with the subject and witnesses. All subjects interviewed for the purposes of the study gave full informed consent. In all cases, individuals had been admitted for diagnostic video EEG monitoring for troublesome nocturnal events of uncertain aetiology, and at least one sleep-related event containing some or all the components of a habitual attack, with full video and EEG data, had been recorded.

In view of the potential problems in accurate diagnosis of NREM parasomnias, which have no 'gold standard' diagnostic test, rigorous inclusion and exclusion criteria were applied to both the parasomnia group and the NFLE comparison group. Subjects with parasomnias were included only if (i) the history was consistent with a diagnosis of parasomnias according to the FLEP scale (see

Chapter 12), and (ii) there was consensus agreement regarding the diagnosis by all clinicians involved in the patient's management (neurophysiologists and neurologists with experience in sleep disorders and epilepsy), following review of the history and all investigations. Subjects were excluded if any diagnostic uncertainty remained despite the recording of events, or if there was any clinical evidence of epilepsy, specifically (i) any history of paroxysmal events suggestive of seizures (other than the nocturnal events under investigation), (ii) epileptiform abnormalities on interical or ictal EEG, or (iii) potentially epileptogenic lesions on neuroimaging. It is recognised that these criteria excluded parasomnia patients with known epilepsy.

A comparison group of 'pure' NFLE subjects was acquired for parallel analysis of semiological and EEG features. Subjects were included in this NFLE comparison group only if they fulfilled the following criteria: (i) the history was compatible with a diagnosis of nocturnal frontal lobe epilepsy according to the FLEP scale; (ii) there was consensus agreement regarding the diagnosis by the clinicians involved in the patient's management (neurophysiologists and neurologists with experience in sleep disorders and epilepsy), following review of the history and all investigations; (iii) at least one of the following biological correlates was present: a potentially epileptogenic frontal lobe lesion on neuroimaging (14% of cases); an established diagnosis of autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE) with a proven genetic mutation (14% of cases); a recruiting ictal rhythm (comprising rhythmic fast, sharp or spike wave activity) on EEG during the episodes (38% of cases); or an ictal SPECT scan demonstrating prominent focal frontal hyperperfusion (43% of cases). NFLE (as opposed to frontal lobe epilepsy *per se)* was only diagnosed if at least 90% of the subject's seizures arose from sleep on the basis of both historical and video EEG monitoring findings. Subjects were excluded if they had either habitual convulsive or diurnal seizures, as such presentations do not cause diagnostic confusion with parasomnias.

Video EEG monitoring

In all parasomnia and NFLE subjects, simultaneous video and EEG data were acquired during the subject's nocturnal events. Video data were captured using

either digital or analogue video cameras; digital or paper EEG was recorded using a minimum of 21 electrodes placed according to the International 10-20 system, with simultaneous single channel ECG. In some patients, data from additional EEG channels, chin EMG and EOG were also recorded.

Ictal EEG findings were categorised as: no change; artefact; partial arousal to lighter sleep; arousal to awake pattern EEG; dissociative pattern (posterior dominant rhythm plus sleep patterns such as theta or delta activity, sleep spindles or vertex sharp waves seen simultaneously); rhythmic slow activity (non-epileptiform); ictal recruiting rhythm; epileptiform ictal discharges (comprising rhythmic sharp or spike wave activity); and other. These ictal EEG categories were not mutually exclusive (i.e. one event could show more than one pattern).

The video EEG monitoring data for each event were reviewed and detailed descriptions recorded. The presence or absence of 68 elemental clinical features was recorded, using a similar approach to that used previously in the analysis of seizure semiology (Manford, 1996; Kotagal et al., 2003). The features included in the analysis were initially generated following analysis of the literature and through clinical experience of the authors, and modified following a pilot study of 9 subjects. These were grouped into the following categories: respiratory; autonomic; simple motor (head, upper limbs, lower limbs, trunk); complex motor (facial, upper limbs, lower limbs); vocal; and others.

The video EEG monitoring recordings were each reviewed and analysed by two observers (the author with Dr Simon Harvey or Dr Matthew Walker). The reviewers were not blinded to the diagnosis, as the study was not designed as a test of diagnostic accuracy. Rather, parasomnias were examined in batch, followed by the NFLE group, to facilitate the reviewers' recognition of common features including behaviours not usually assessed in seizure analysis. As some subjects in the NFLE group had large numbers of events recorded, with the potential to distort a quantitative analysis, a maximum of three seizures per subject were analysed in this group. In patients with more than three recorded seizures, data from the first three clearly recorded seizures only were included in the study.

In addition to the video and EEG features, the number of events in total and the maximum number of events per night were recorded for each subject. For each event, the duration of the episode, as well as the duration of any arousal behaviours preceding the major motor behaviour, was recorded. In view of the fact that parasomnias are often said to be ameliorated by sleeping in unfamiliar environments (Jacobson et al., 1965; Joncas et al., 2002), the proportion of individuals in each group in whom events occurred on the first night of monitoring was documented.

Statistical Analysis

Elemental clinical features. For the elemental clinical features, data for a binary outcome (parasomnias or NFLE) were analysed using logistic regression. For each subject, the number of events was the denominator and the number of events showing the feature of interest was the numerator. This ensured statistical independence between the observations analysed, effectively generating a single observation for each subject irrespective of the number of events recorded. The explanatory variable fitted by this analysis was diagnosis (i.e. NFLE or parasomnia); the test of significance gave a p-value for the strength of the association between the feature and diagnosis, and the odds ratio indicated the direction of the association.

For some variables, one group did not display a particular feature in any events. Logistic regression fails for these variables, since it relies on large sample approximations in which the estimated odds ratios are neither zero nor infinity. In such cases, the association between the group and the feature of interest was analysed by recording whether a subject showed the feature of interest in any event, and then using Fisher's exact test to compare between NFLE and parasomnias. As for logistic regression, this approach assesses the strength of association at the "subject" level, not the "event" level, preserving statistical independence between the observations.

For the continuous variables (e.g. time to major motor behaviour, duration of event etc), median values were obtained for each subject. The means were compared between NFLE and parasomnia groups using the Mann-Whitney U test.

As recommended by several authorities (Rothman, 1986; Perneger, 1998), no statistical adjustments were made for multiple comparisons in these analyses, but the dataset is presented in its entirety with the results of all comparisons displayed.

Cluster analysis and decision tree. To identify the natural grouping of NFLE seizures and parasomnias according to their elemental clinical features, and to examine the degree of overlap between them, statistical cluster analysis was performed on the 120 events from the video EEG/ polysomnography data, based on the presence or absence of the elemental features (Table 1). The analysis was performed on Statistical Package for Social Sciences (SPSS) software using Ward's method with Euclidean squared distance measurements; this is a hierarchical cluster technique which has previously been adopted in studies of seizure semiology (Manford, 1996). Internal validation was undertaken using a k-means cluster analysis, an alternative, non-hierarchical cluster analysis technique.

Using the individual elemental clinical features identified from the video recordings of each event, a model for classification was generated using the exhaustive CHAID decision tree algorithm (Biggs, 1991) performed with the Statistical Package for Social Sciences (SPSS) Answer Tree 3.0 software.

Results

Video EEG monitoring data from 120 nocturnal events in 44 patients were studied. The study group comprised 57 NREM parasomnias from 23 subjects (14 males) and the comparison group comprised 63 NFLE seizures from 21 subjects (13 males). The median age of onset for parasomnias was 8.5 years (range 1.5 - 39 years) and for NFLE was 7.0 years (range 0.5 - 34 years). Median age at the time of video monitoring was 12 years (range 4 - 69 years) for the NREM parasomnia group and 21 years for the NFLE groups (range 3 - 38 years). Fifteen of the 23 parasomnia cases and 10 of the 21 NFLE subjects were children (under 18 years).

Individuals in the parasomnia group had a median of two events in total during the monitoring period, compared to 8 for NFLE subjects ($p<0.001$); the median duration of monitoring was 3.5 nights. 42% of parasomnia subjects had events on the first night of monitoring compared to 76% of NFLE subjects ($p=0.03$).

The median maximum number of events recorded per night was 2 (range 1-5) in the parasomnia group and 7 (range 1-10) in the NFLE group ($p<0.001$). Median event duration was significantly longer in the parasomnia group (60 seconds, range 11 seconds - 14 minutes) than the NFLE group (37 seconds, range 9 – 125 seconds; $p<0.001$). 27% of parasomnias lasted over two minutes; 44% lasted less than a minute. In NFLE, the historical accounts of individuals' seizures were very similar to recorded events in terms of both attack duration and component features. This contrasted with parasomnias, in which monitored events were often shorter and less elaborate than those described in the history.

Both parasomnias and seizures arose exclusively from NREM sleep. Seizures tended to be from lighter stages (9% stage 1, 79% stage 2 and 13% stage 3) in comparison to parasomnias (all from stage 3 or 4). Definitive ictal thythms were seen in 38% of NFLE subjects, although this figure may be artificially high due to our incusion criteria (see Methods). In 52% of individuals with parasomnias, light sleep patterns (vertex waves, sleep spindles and theta activity) were seen at some point during events; in a subgroup of these (27% of cases) evidence of state

dissociation was seen at some point, with posterior dominant alpha rhythm suggestive of resting wakefulness in posterior electrodes but anterior theta activity, sometimes with vertex waves or spindles, consistent with light sleep (Figure 13.1). These findings were not seen in NFLE seizures.

Other findings showed considerable overlap between NFLE and parasomnias, and did not significantly favour one condition or the other. Muscle and movement artefact were prominent in both, in some cases obscuring cerebral rhythms; rhythmic non-epileptiform theta or delta activity over the anterior quadrants was commonly observed in both conditions (61% parasomnias, 52% NFLE; p=0.36); diffuse attenuation in EEG amplitude, a manifestation of seizure onset or state change, was also seen frequently in both groups (43%NFLE, 39% parasomnias; p=0.64).

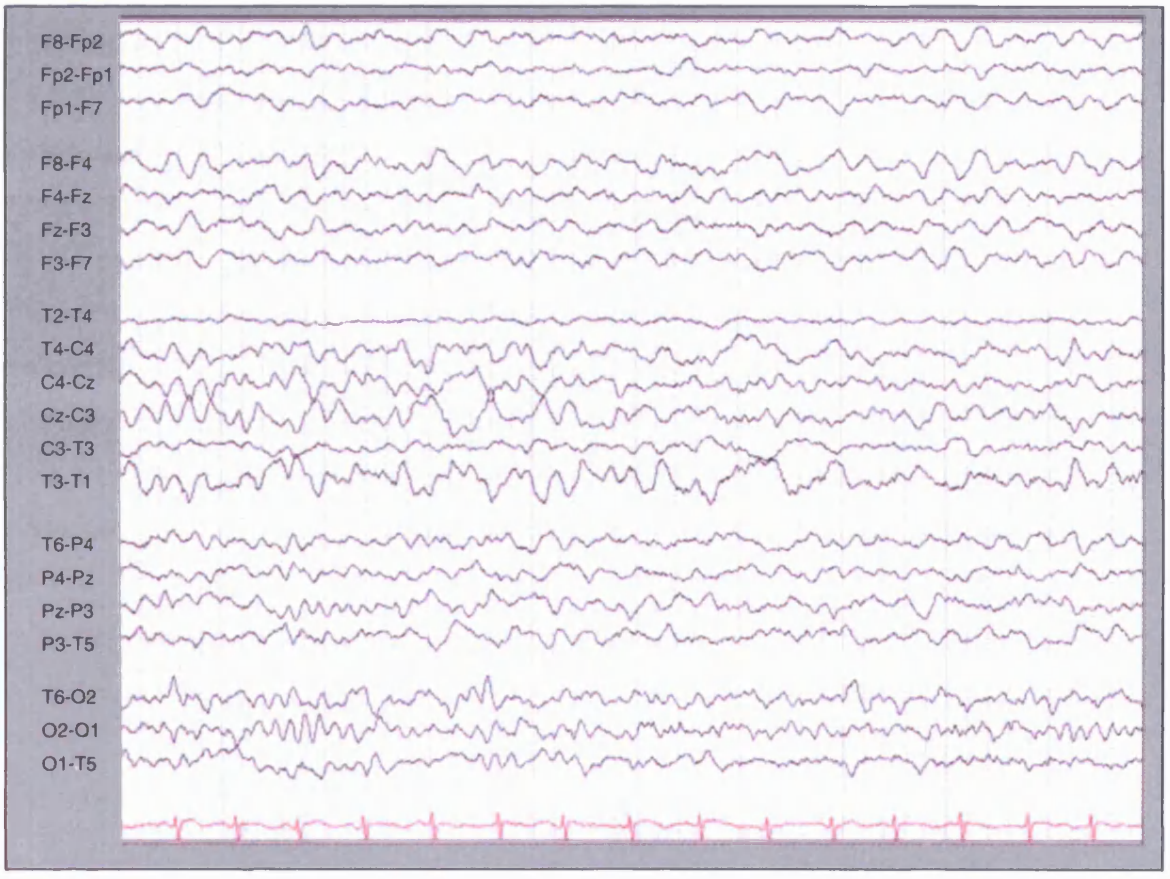


Figure 13. 1 *EEG (transverse montage) during a prolonged parasomnia, showing a dissociation pattern; a clear alpha rhythm is seen in posterior channels consistent with the subject's posterior dominant rhythm, with anterior and midline theta activity and vertex sharp waves consistent with light NREM sleep .Timescale is 1 page = 10 seconds.*

1. Statistical analysis

Elemental clinical features. The frequencies of individual elemental clinical features in parasomnias and NFLE are summarised in Table 13.1, along with comparative statistics. The features that most strongly favoured a diagnosis of parasomnias were crying or sobbing, a waxing and waning quality, modification of the event by individuals in attendance, coherent speech in sentences, and normal arousal behaviours such as face and nose rubbing, scratching and rolling over in bed. In contrast, bicycling movements, thrashing, grunting, grimacing and dystonic posturing, all common in NFLE, were very infrequent in parasomnias.

Cluster analysis and decision tree. Ward's cluster analysis generated two major groups of event from the 120 individual episodes examined. These groups were identified through visual inspection of the dendrogram output of the analysis, and through graphical examination of the cluster coefficient against cluster number; while the gradient of this plot increased gradually with decreasing cluster numbers, it increased substantially when the number of clusters fell from two to one, suggesting the correct number of natural clusters was two. Internal validation using k-means analysis was subsequently performed for two clusters; there was 97% concordance in the clustering of cases using these two techniques. The two major clusters identified corresponded to an NFLE group and a parasomnia group. Overall, 91% of events were correctly classified using Ward's method, (90% using the k-means cluster technique). Using the Ward method, within the NFLE cluster 98% of events were true NFLE seizures (96% using k-means analysis); within the parasomnia cluster, 85% were true parasomnias (84% using k-means analysis).

The diagnostic classification tree, based on the video features of events only, is shown in Figure 13.2. In our dataset this algorithm correctly classified 113 of 120 (94%) nocturnal events. The model therefore has a 6% misclassification risk (SE= 0.02).

As the elemental clinical features alone do not adequately portray the semiology of parasomnias, a detailed description is provided below, comprising details of event onset, evolution, and offset, followed by a summary of the fundamental

Clinical Feature	%age of NFLE events	%age of parasomnia events	B	Wald χ^2 statistic	odds ratio	p value*
scratching	2%	23%	2.9	7.6	18	<0.001
crying or sobbing	2%	21%	2.8	7.0	16	<0.001
waxing and waning quality	0%	39%	n/a	n/a	n/a	<0.001
"settling" behaviours after episode (adjusting position etc)	32%	85%	2.6	30	13	<0.001
event modified by people in the room (ended/ exacerbated)	4%	35%	2.4	13	11	<0.001
verbal interaction with individuals in attendance	4%	35%	2.1	13	8.0	<0.001
rubbing (nose or face)	25%	70%	1.9	22	6.9	<0.001
coherent speech (sentences of more than 2 words)	5%	32%	1.9	11	6.8	<0.001
periods of motionless staring	22%	60%	1.6	16	5.2	<0.001
rolling over in bed	11%	39%	1.6	11	5.0	<0.001
pleading behaviours and speech	2%	18%	2.6	5.8	13	0.001
mumbling/ incoherent speech or single words	7%	30%	1.8	9.6	6.2	0.001
manipulation of objects or clothing	16%	42%	1.4	9.5	3.9	0.001
coughing	2%	16%	2.5	5.2	12	0.003
myoclonic jerks	2%	12%	2.2	4.0	8.7	0.01
moaning or groaning	8%	25%	1.3	2.4	3.8	0.01
clear external environmental trigger (e.g.noise)	6%	21%	1.3	5.0	3.9	0.01
physical interaction with people	11%	30%	1.2	6.1	3.4	0.01
looking around	49%	72%	1.0	6.3	2.7	0.01
rubbing body or limbs (not face)	6%	21%	1.4	5.0	3.9	0.02
yawning	0%	19%	n/a	n/a	n/a	0.02
physical interaction with objects	11%	30%	0.83	4.5	2.3	0.03
kneeling	3%	12%	1.5	3.1	4.2	0.05
chewing	6%	18%	1.1	3.4	3.1	0.05
sitting up	46%	65%	0.61	3.0	1.9	0.08
axial flexion (any)	63%	77%	0.67	2.6	2.0	0.1
shouting	6%	14%	0.88	1.9	2.4	0.2
tremor or trembling/ shivering	3%	9%	1.1	1.6	2.9	0.2
sighing	0%	9%	n/a	n/a	n/a	0.2
pelvic thrusting movements	5%	10%	0.86	1.4	2.4	0.2
clonic jerking	12%	0%	n/a	n/a	n/a	0.2
complex and directed behaviours	19%	28%	0.51	1.4	1.7	0.2
stiffening (not dystonic – includes stretching)	51%	40%	-0.42	1.2	0.7	0.3
trunk hyperextension	7%	3%	-0.83	0.90	2.3	0.3
wiggling/ wriggling, lower limb	44%	51%	-0.3	0.66	0.7	0.4
wiggling/ wriggling, upper limb	65%	57%	0.26	0.49	1.3	0.5
foot stamping	2%	4%	0.81	0.44	2.3	0.5
holding/ hugging (people or objects)	20%	15%	-0.33	0.46	0.7	0.5
head elevation	75%	79%	-0.24	0.31	1.3	0.5
screaming	10%	12%	-0.28	0.23	1.3	0.6
sad/ unhappy expression	20%	18%	-0.20	0.19	0.81	0.7
fearful expression	43%	46%	-0.11	0.09	1.1	0.8
searching behaviours	19%	21%	-1.3	0.07	1.1	0.8
walking	3%	2%	-0.61	0.24	0.51	0.6
standing	10%	5%	-0.64	0.76	0.49	0.4
head nodding	5%	2%	-1	0.80	0.40	0.4
agitated quality to event	67%	56%	-0.44	1.4	0.61	0.2
swallowing	0%	7%	n/a	n/a	n/a	0.2
punching or hitting	10%	4%	-1.1	1.6	0.40	0.2
head shaking	13%	5%	-0.96	1.9	0.41	0.2
highly repetitive behaviours within an event	44%	26%	-0.81	4.2	0.50	0.04
apnoea/ stopped breathing	29%	0%	n/a	n/a	n/a	0.02
marked asymmetry	27%	0%	n/a	n/a	n/a	0.02
writhing or choreoathetoid movements	29%	0%	n/a	n/a	n/a	0.02
eyes open during episode	97%	84%	-1.7	4.7	0.2	0.01
head version	22%	0%	n/a	n/a	n/a	0.004
no change from onset position	46%	19%	-1.2	9.2	0.30	0.002
axial twisting movements	36%	11%	-1.6	9.9	0.20	0.001
dystonic stiffening/ posturing	49%	0%	n/a	n/a	n/a	<0.001
kicking	29%	5%	-2.0	9.1	0.14	<0.001
hyperventilation	52%	12%	-2.1	18	0.13	<0.001
rocking movements	33%	5%	-2.2	11	0.11	<0.001
grimacing	33%	4%	-2.6	12	0.07	<0.001
sudden, clear offset	76%	16%	-2.8	37	0.06	<0.001
hyperkinetic thrashing	27%	2%	-3.0	8.3	0.05	<0.001
grunting respirations	52%	0%	n/a	n/a	n/a	<0.001
apparent full wakefulness after event	88%	26%	-3.1	38	0.04	<0.001
cycling movements	33%	2%	-3.3	10	0.04	<0.001

Favours Parasomnia

Favours NFLE

Table 13. 1. *Frequencies of elemental semiological features recorded in parasomnias and NFLE. The table is ordered according to the strength of association of each feature to diagnosis. Raw percentages of events in each group showing the feature are given. The statistical significance of these values, according to binary logistic regression or Fisher's exact test, accounts for the number of events in each subject as described in the methods section. The logistic regression coefficient (B), Wald statistic, odds ratio and uncorrected p values are given for those elemental features analysed using logistic regression. For those assessed using Fisher's exact test, p values only are given. Light shading represents p values of 0.05 – 0.001; dark shading represents p values of < 0.001.*

behavioural patterns observed. Although the features of parasomnias are contrasted with the NFLE comparison group, the clinical features of the NFLE group are not discussed in detail as this condition has been thoroughly described elsewhere (Williamson, 1995; Provini et al., 1999); our findings were consistent with previously published reports.

2. Temporal aspects of parasomnias

(i) Event onset.

Parasomnia onsets usually comprised (79% of events) 'normal' arousal, with stirring, opening the eyes, head elevation and looking around or staring. This lasted from one or two seconds to several minutes, and in 65% of cases was followed by more dramatic manifestations. Less commonly (21%), there was explosive motor behaviour with apparent fear or agitation at onset. This typically comprised sitting forward with a frightened expression, often with agitated searching behaviours (the typical 'sleep terror' pattern). Usually this onset was associated with distressed and coherent, but simple, speech ("help me", "what's happening", "mum" etc).

Regardless of the type of onset, tachycardia was almost universal; there tended to be a greater increase in heart rate in the 'sleep terror' onset, with often a doubling of heart rate, and the degree of tachycardia was greatest in young children. Onset was triggered by a clear external stimulus such as a noise or an internal stimulus such as a cough or snore in a considerable proportion of parasomnias (39% in total – **see video 13.1 and 13.2**).

Comparison with NFLE. A brief arousal, indistinguishable from that seen in parasomnias, also preceded the major behaviours in 49% of NFLE seizures (p=0.10; see **video 13.3**); this was of comparable median duration in the two conditions (approximately 7 seconds). An abrupt onset with no preceding arousal was seen in 51% of NFLE seizures (**video 13.4**), although fearful behaviour was not invariably a feature of these events. As with parasomnias, NFLE seizures

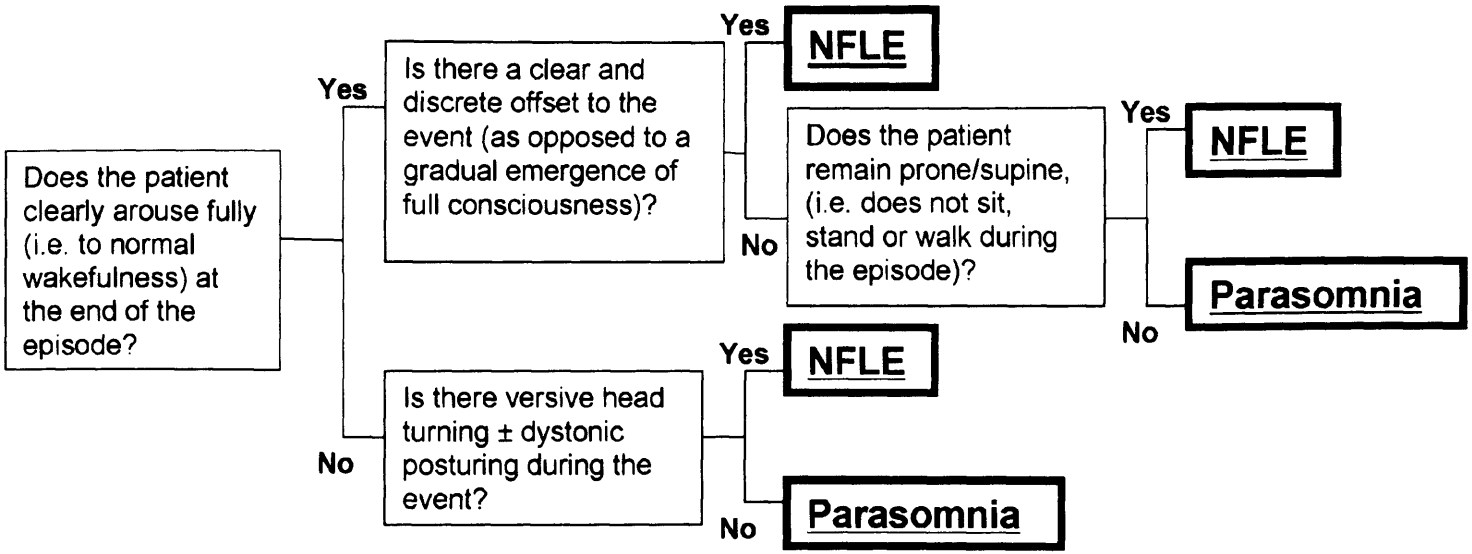


Figure 13. 2. *Results of the exhaustive CHAID Tree Analysis for the diagnosis of nocturnal events. This algorithm correctly identified 94% of the 120 nocturnal events in the study.*

were universally associated with tachycardia. However, obvious triggers such as noise were seen in only 8% of seizures.

(ii) Progression

There was often evidence of increasing interaction during the episode (**video 13.5**). At onset, typically minimal physical interaction was seen, and speech was absent or limited to brief simple phrases. As the event progressed, however, hugging or holding of people nearby, semipurposeful behaviours, and more complex interactive speech were increasingly seen. Moreover, over one third of parasomnias appeared to be modified (either exacerbated or terminated) by the actions of other persons who were present. Secondly, a waxing and waning pattern of motor activity and emotional distress was observed in 39% of events (**video 13.5**).

Comparison with NFLE. Environmental interaction was less prominent in NFLE. While present in 11% of seizures, it was usually simple (repeatedly grabbing at bed sides or occasionally a person in attendance), and did not increase through the event.

Coherent speech was unusual in NFLE, and tended to be frenetic and agitated without a discernable interactive quality (Table 13.1; **video 13.4**). Likewise, a waxing and waning pattern was not seen in NFLE seizures which tended to be monophasic.

(iii) Event offset.

Parasomnias terminated with either full arousal to normal wakefulness (26%) or to light NREM sleep (74%). A clear and distinct offset was uncommon (16% of events). Subjects showingf NREM sleep at offset usually progressed rapidly back to deep slow wave sleep. In parasomnias terminating in wakefulness, the precise point at which full 'normal' consciousness was reached was difficult to determine (**video 13.5**), and for those events without full wakefulness a 'tapering off' of motor behaviour was seen with gradual settling back to sleep. A few parasomnias (9%) ended with the patient waking fully, leaving the bed and urinating. Although

not seen in most events, this behaviour may reflect autonomic activation, or implicate a full bladder in the initial arousal stimulus. Incontinence was not observed.

Comparison with NFLE. The offset pattern in NFLE was strikingly different to that of parasomnias, with 88% of seizures ending in full wakefulness. All seizures with florid automatisms ended in wakefulness; the only events that did not were those characterised by brief dystonic posturing only. Likewise, a distinct offset was usually seen in NFLE seizures (76%). A brief postictal period was sometimes seen, and when present the behaviours observed were qualitatively very similar to those in parasomnias (**video 13.6**). No seizures ended with the subject waking and urinating, and no incontinence was seen.

3. Fundamental behaviour patterns in parasomnias

A relatively narrow repertoire of behaviours was seen during parasomnias, and many events were very similar in onset and progression. Overall, three fundamental patterns of behaviour were seen, and most individual events (79%) comprised a composite arrangement of more than one of these.

The first pattern resembled normal arousal behaviours. These were seen at some point in almost all events (92%). They typically occurred around onset or towards the end of the episode, but in some events were the only feature. The basic arousal behaviours were eye opening, head elevation, looking around and staring (**video 13.7**). However, more elaborate behaviours were also seen; in particular, prominent and often vigorous rubbing of the nose or face, yawning, rolling over in bed and scratching of the head or body often became prominent as the event progressed, sometimes associated with moaning and incoherent speech or mumbled single words. Also, in some cases myoclonic jerks and trembling or shivering were seen. Normal hypnic jerks appeared to precipitate some parasomnias; in other events tremor and shivering were seen intermittently during the event (**videos 13.8 and 13.2**). These were rare in NFLE.

The second pattern comprised non-agitated motor behaviour and was seen at some point in 72% of events. Sitting forward, manipulation of objects in the immediate vicinity, and searching behaviours (looking over the side of the bed, under pillows etc) was seen. Facial expression was impassive, although sometimes individuals looked perplexed. More directed behaviours such as pointing at things (real or imagined), hand licking, looking under bedclothes, and picking up and manipulating EEG equipment or objects around the bed (taking tissues from a box, opening water bottles etc) were also observed (**videos 13.1 and 13.9**). Usually these directed behaviours were brief in duration, lasting for 10-15 seconds. Although standing and walking on the bed were occasionally observed during this phase (**video 13.10**), no frank somnambulism was seen as subjects were restrained by EEG equipment or individuals in the room. Speech, sometimes mumbled and unintelligible, but more typically coherent, was also common. A clear interactive component to speech and behaviour was frequently observed during this pattern (44% of events).

The third pattern comprised distressed emotional behaviour (51% of events). This typically comprised fearful, agitated behaviours and facial expressions. Sitting or standing, screaming, frantic looking around, recoiling or evasive behaviours from a perceived or imagined threat, and negative or fearful speech ('they're going to kill me", "I'm going to die") were prominent (**videos 13.11 and 13.12**). During this pattern, attempts to console or restrain the subject were often resisted, and sometimes provoked aggressive behaviour such as hitting or foot stamping. In other events, inconsolable sobbing and anguish, often with wailing and pleading speech (such as "mum, help me, please"), were prominent (**video 13.13**) rather than fear and agitation. Notably, the central behaviours in this pattern were of negative emotions, either fear or anguish, with concordant facial expression, speech and motor behaviour.

The three behaviour patterns occurred in various combinations and sequences in individual events, with some hierarchy as shown schematically in Figure 13.3. These were broadly but not entirely congruent with the traditional subclassifications of NREM arousal parasomnias. The first combination (19% of events; Figure 13.3, panel (35% of recorded events; Figure 13.3 panel ii) often

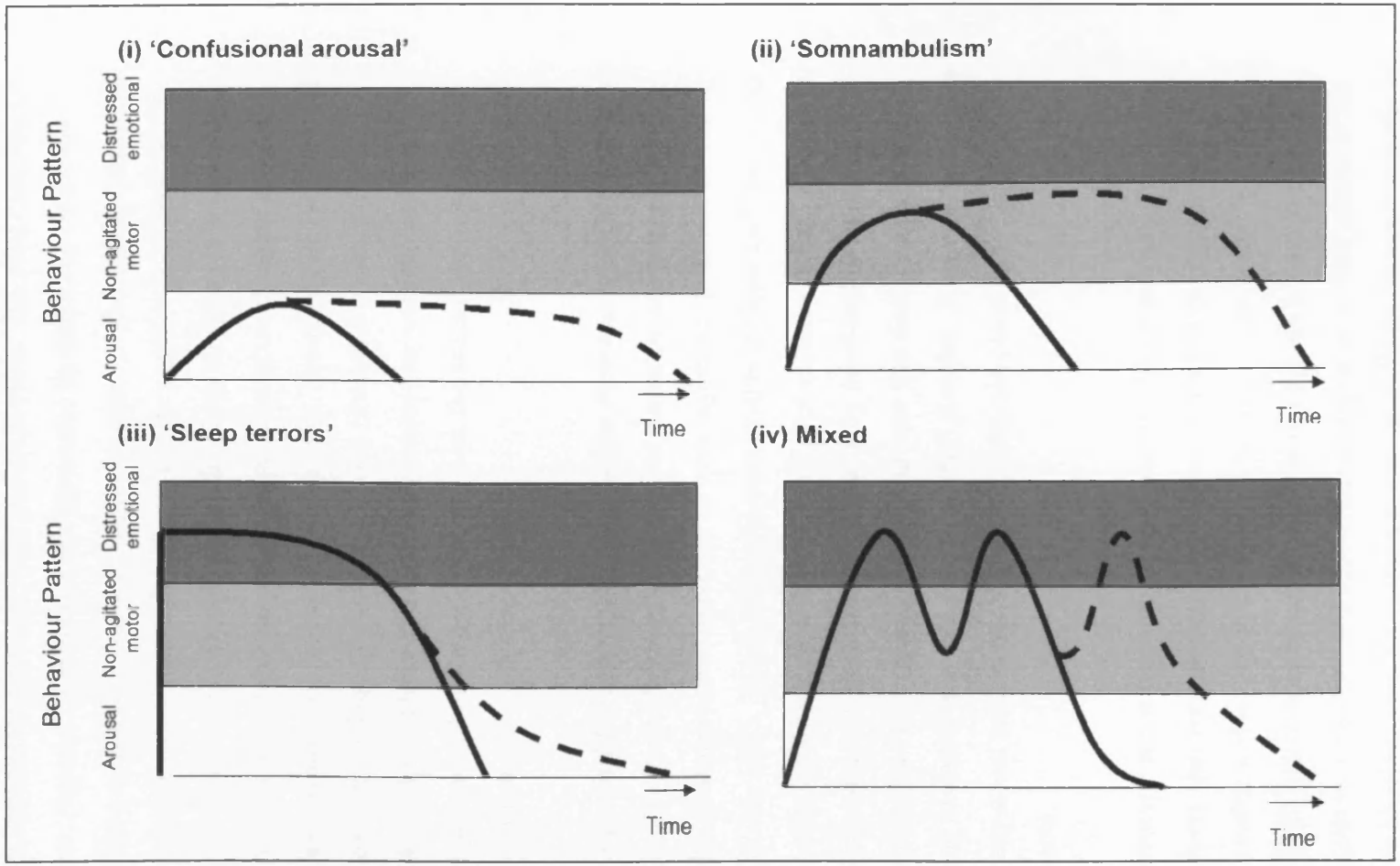


Figure 13.3. *Schematic representation of common parasomnias, displayed as hierarchical combinations of the three fundamental behaviour patterns on the y axis, and time (typically 1-10 minutes) on the x axis. Panel (i) represents a typical confusional arousal, comprising only normal arousal behaviours but of abnormal duration (19% of recorded events); panel (ii) shows classical somnambulism with non-agitated motor behaviour, and normal arousal behaviours at onset, offset or both (35% of recorded events); panel (iii) represents typical sleep terrors, with predominantly negative emotional behaviour often of sudden onset; calm motor and normal arousal behaviours are usually also seen during these events, either at onset or offset (26% of events); panel (iv) is a mixed type, but comprising waxing and waning of the four behaviour types (19% of events). All events usually start in stage III or IV NREM sleep, and end either in wakefulness or lighter NREM sleep. Sometimes episodes are brief (solid lines) and at other times prolonged (hatched lines).*

started and ended with arousal behaviours, but non-agitated motor behaviours and speech predominated. Although frank sleepwalking was not seen in this series, these episodes appeared to represent early somnambulism. The third combination (26% of events; Figure 13.3 panel iii) was dominated by distressed emotional behaviour. These events could have an explosive onset, and would be classically described as 'sleep terrors', although fear was not the negative emotional behaviour in all these events. The fourth and final combination (19% of events; Figure 13.3 panel iv) observed was not classifiable using the classical subtypes. These episodes contained all four behaviour patterns, alternating in a waxing and waning fashion over a relatively prolonged period of several minutes (in some cases up to 14 minutes). Distressed emotional behaviours were the striking features of these events, but were interspersed with the arousal and non-agitated motor behaviour patterns.

Comparison with NFLE. The behavioural patterns were usually different to those seen in NFLE. The more elaborate behaviours of parasomnias (such as yawning and nose rubbing) were unusual in NFLE, as were myoclonic jerks and trembling or shivering (Table 13.1). While distressed emotional behaviour could be seen in NFLE, it was often qualitatively different to that seen in parasomnias. The fearful or distressed behaviours in parasomnias were usually more highly emotive, whereas grimacing and undirected frenetic behaviour was more common in NFLE; sobbing or crying were not seen in our NFLE series. However, sometimes the negative emotional behaviours in the two conditions could be indistinguishable.

Although stereotypy is a widely recognised feature of NFLE seizures, many parasomnias were also very similar. The behaviour patterns described were usually very similar within, and to some extent between, individuals. However, in contrast to NFLE, behaviour patterns in parasomnias did not always follow a consistent sequence; patterns could appear and disappear at various phases in the event, with the sequence varying between events, or could be 'skipped' entirely in some episodes.

Discussion

This study, to my knowledge, represents the largest reported group of NREM parasomnias studied with video EEG monitoring, and the only detailed semiological analysis of these conditions. The landmark neurophysiological studies of parasomnias in the 1960s included broad clinical descriptions of the attacks, but were performed prior to the advent of video EEG monitoring and did not address semiology in detail. They were also performed prior to the recognition of the spectrum of clinical features seen in frontal lobe epilepsy, and the appreciation of NFLE as a distinct syndrome.

Rather than identifying the classic parasomnia subtypes of sleep terrors, somnambulism and confusional arousals, we identified four key behavioural patterns which could combine in a variety of forms. These comprised normal arousal behaviours, non-agitated motor activity, apparent fear, and distressed sobbing. From a diagnostic perspective, the most important findings were that parasomnias and NFLE usually have distinct presentations, and can be distinguished on the basis of objective statistical analysis. However, both conditions may have very similar onset patterns with non-specific arousal behaviours, indicating that it may not be possible to diagnose very brief events on the basis of semiology alone.

A. Methodological Considerations

In a study of this type the inclusion and exclusion criteria applied are critical. This is of particular importance for the parasomnias, which are quasi-physiological phenomena with no definitive biological marker to serve as a 'gold standard' in diagnosis. In addition, NFLE, is often associated with normal or non-diagnostic investigations; even ictal EEG is often unhelpful (Provini et al., 1999). This study, therefore, ran the risk of circularity – in other words, the clinical and EEG findings described might simply be the features used by observers to define the groups, making the study self-fulfilling. We sought to avoid this through the adoption of stringent exclusion and inclusion criteria. NFLE cases without definite biological correlate (such as an ictal rhythm on EEG or a positive SPECT scan) were

excluded, to ensure that the diagnosis in this group was indisputable; individuals with convulsive and diurnal seizures were also excluded, to ensure that the comparison group accurately reflected the NFLE seizures which cause diagnostic confusion in clinical practice.

While minimising the risk of misdiagnosis cases, this selection strategy raises the possibility (by excluding equivocal or uncertain events) of artificially separating NFLE and parasomnias, and thereby not reviewing the full spectrum of nocturnal events. The issue of isolated brief arousals from sleep is particularly relevant here and is discussed later.

B. Practical differences between NFLE and parasomnias on video EEG monitoring: useful features and potential pitfalls.

Cluster analysis, based purely on the presence or absence of elemental behaviours, divided these nocturnal events relatively cleanly into seizures and parasomnias. This indicates that there are broad behavioural differences between these conditions, although the fact that 15% of seizures were grouped with parasomnias confirms a degree of overlap. The clinical 'decision tree', which generates a diagnostic model using those features of greatest discriminatory value, is shown in Figure 13.2. This provides a practical framework for analysing video recordings of nocturnal events, and in our series correctly identified 94% of cases. Failure to rouse to full wakefulness, an indistinct end to the events, and a lack of dystonic posturing and head version were the most powerful indicators of parasomnias in this analysis. The algorithm may be useful in the assessment of nocturnal events in both the seizure monitoring laboratory and home videos, although prospective validation has yet to be undertaken.

Several other characteristics of the onset, progression and offset of parasomnias which may be useful in their positive diagnosis were also identified in this study, documented in detail in Table 13.1 and summarised in Table 13.2. In particular, clear triggers (either internal or external) at onset, elaborate features of normal arousal (such as nose rubbing, scratching, and yawning), clear verbal or physical

Features strongly favouring parasomnias	Features moderately favouring parasomnias	Features which do *not* discriminate between parasomnias and NFLE
Yawning	Tremor/ trembling	Brevity
Scratching and prominent nose-rubbing	Myoclonic jerks	Sitting
	Coughing	
Rolling over in bed	Semipurposeful behaviours, fumbling, manipulation of nearby objects	Standing or walking
Internal or external trigger (noise, cough, snore)	Variability/ absence of stereotypy	Preceding 'normal' arousal
Waxing and waning pattern	No events recorded on first night of monitoring	Brief arousals (up to 10 seconds) without definite semiological features of epilepsy
Physical or verbal interaction	Few events recorded in total (less than 3)	
Sobbing, sad emotional behaviour		Fearful emotional behaviour
Indistinct offset		
Failure to fully arouse after event with complex behaviour		
Prolonged duration (>2 minutes)		
Discordance between severity and duration of *reported* event and *recorded* event		

Table 13. 2. *Important quantitative and qualitative features which can be used in the positive identification of parasomnias.*

interaction, and a prolonged duration (over 2 minutes), all favour a diagnosis of parasomnias over NFLE.

In general, despite the variety of behaviours reported in the histories of parasomnia subjects, the behavioural repertoire observed in our series was relatively small. The abnormal and restrained environment of the video EEG monitoring environment may restrict expression and elaboration of more complex behaviours (including somnambulism) fleetingly recorded in some individuals. Discrepancies between the historical account and recorded events, particularly in terms of event severity, was a prominent feature in our parasomnia group, in contrast to the NFLE group in whom the history and video EEG monitoring were generally concordant (as recognised in previous studies (Manford, 1996)).

A number of important potential diagnostic pitfalls in the assessment of nocturnal events should be addressed at this point. Firstly, an important consideration is the diagnosis of recurrent, brief arousals from sleep. Such events are well recognised in NFLE, where they are typically highly stereotyped and are regarded as 'fragments' of the habitual seizures (Montagna et al., 1990; Zucconi et al., 1997; Provini et al., 1999; Provini et al., 2000; Valenti et al., 2006). Intracerebral recordings have confirmed that these arousals may be associated with brief electrographic seizures without scalp EEG changes (Nobili et al., 2005), and that seizure onset in sleep may precede clinical arousal and motor behaviour by up to 15-20 seconds (Malow and Varma, 1995). However, many other, non-epileptic conditions such as restless legs syndrome or obstructive sleep apnoea, may also cause recurrent arousals. As a result, when recurrent arousals with no distinguishing motor behaviours or accompanying ictal rhythms are captured, it can be extremely difficult to ascertain whether they have an epileptic basis. Because of these diagnostic difficulties, such cases were not included in this study. Despite this, our observations suggest that their accurate diagnosis may not be possible on semiological grounds alone. The brief periods of 'normal' arousal behaviours seen in both groups, which often preceded the main motor behaviour of the event, were indistinguishable in NFLE and parasomnias (**videos 13.3, 13.7**) suggests that additional information is necessary to make an accurate diagnosis. Stereotypy and frequency are generally considered to be the most useful pointers

to a possible epileptic origin when other investigations are unhelpful in such situations (Oldani et al., 1996; Zucconi et al., 1997; Zucconi and Ferini-Strambi, 2000; Tinuper et al., 2004). However, our findings suggest that while marked stereotypy of arousals is suggestive of epilepsy, this feature does not invariably indicate such a diagnosis; the onset of parasomnias could be similarly stereotyped. Secondly, postictal behaviours, albeit usually very brief (lasting less than one minute), were seen in a proportion of NFLE subjects, and when present were strikingly similar in quality and nature to parasomnias. Staring, looking around, semipurposeful fumbling and partially interactive speech were all seen in this postictal period (**video 13.6**). From a practical perspective it is important to bear this in mind when reviewing videos, particularly home videos, in which the onset of a nocturnal event may not have been captured. If the entirety of the episode is recorded, however, a clear distinction between ictal and postictal behaviours is usually possible in NFLE.

Finally, it is important to fully consider the range of nocturnal events in sleep. While NFLE and NREM parasomnias are often the most difficult conditions to distinguish, other parasomnias such as REM behaviour disorder should also be considered in the differential diagnosis, along with non-epileptic conditions such as obstructive sleep apnoea, gastro-oesophageal reflux and nocturnal panic disorder (see literature review, Chapter 10 for full discussion).

C. Parasomnias - Broad concepts.

Although NREM arousal parasomnias are traditionally grouped into three distinct types (confusional arousals, sleep terrors and somnambulism), the results of this study only partially support this classification. Rather, they suggest that several basic behaviour patterns occur in parasomnias, and that individual events comprise a mixture of these. The patterns occur in a hierarchical fashion, with normal arousal behaviours being the fundamental component; almost all events contained these behaviours at some stage. The next level of behaviour is abnormal but non-agitated motor behaviour; presumably this would include somnambulism, although this was not recorded in this study. The third, and most abnormal, tier on

the hierarchy is negative emotional behaviour, either fearful and agitated or distraught and tearful in nature. Although any one of these patterns could predominate, they would not occur in isolation; components from the level below would always be present at some stage. In other words, while an event could comprise arousal behaviours alone, calm motor behaviours were not seen without arousal features, and agitated activity was not seen without both arousal features and calm motor behaviours. The sequence of these behaviours could, however, vary significantly between individuals, and between episodes in individual subjects.

This hierarchy has led us to a clinical concept of parasomnias based on two axes, behaviour and time, shown in Figure 13.3. Although any combination within this framework appears possible, and different combinations could be seen within a single individual, 4 main combinations were observed as shown. Although these were broadly consistent with the recognised subclassifications of NREM arousal parasomnias, our findings suggest that labelling individual events as sleep terrors, somnambulism or confusional arousals is an oversimplification. Rather, abnormal arousal behaviour has three main components (prolonged normal arousal, non-agitated motor behaviour, and distressed emotional behaviour) the balance of which may vary between individual events.

D. Theoretical implications - parasomnias

Current concepts of the NREM arousal parasomnias have changed little since the landmark studies of Gastaut and Broughton in the 1960s (Gastaut, 1965; Broughton, 1968). They are broadly considered to represent a functional deafferentation of the cerebral cortex in which brainstem and thalamic arousal processes are dissociated from normal awake cortical function and consciousness (Broughton, 1968), and more recent work has largely supported this hypothesis (Bassetti et al., 2000; Balkin et al., 2002). They appear to arise through a combination of unusually intense slow wave sleep, which makes arousal to wakefulness difficult (Espa et al., 2000; Joncas et al., 2002), and sleep instability (Zucconi et al., 1995), possibly related to frequent arousals due to obstructive sleep apnoea in some individuals (Espa et al., 2002; Guilleminault et al., 2005).

The very high incidence of NREM parasomnias during childhood (Laberge et al., 2000; Agargun et al., 2004) suggests that maturation and synchronisation of various central arousal mechanisms may play a role in these disorders (Sheldon, 2000). Three observations in the current study are relevant to the pathophysiology of NREM parasomnias.

Firstly, the high proportion of clear triggers to events is consistent with a disordered response to arousal stimuli, either internal (such as coughing, snoring and hypnic jerks) or external (particularly sudden noises). In the normal situation such stimuli would be followed by full wakefulness or a return to sleep; however, in predisposed individuals, incomplete arousal results in a dissociated state which manifests clinically as a parasomnia. This initiation of parasomnias by internal triggers explains the emerging data that obstructive sleep apnoea may be a significant factor in some individuals with NREM arousal parasomnias (Guilleminault et al., 2005).

Furthermore, the nature of initial arousal behaviour, when present, was indistinguishable in parasomnias and NFLE, and impossible to differentiate from normal waking arousal. This suggests that such behaviours represent a common non-specific response to a stimulus during sleep; this stimulus can be 'normal' (e.g. a loud noise) or pathological (e.g. a subclinical seizure), but either will result in the same initial arousal behaviour (Figure 13.4). In the case of NFLE, a brief subclinical seizure may be a sufficient stimulus to generate such a non-specific arousal response without necessarily progressing to a clinical seizure. This concept would explain recent findings from intracranial electrode studies in NFLE, in which paroxysmal arousals associated with brief seizures were not highly stereotyped (Nobili et al., 2005); in these cases the seizure is apparently a sufficiently large stimulus to produce a non-specific arousal from sleep, but is not prolonged or widespread enough to produce seizure-specific behavioural manifestations. It might also explain occasional reports of parasomnia-like wandering in individuals with NFLE (Plazzi et al., 1995); it seems possible that in predisposed individuals, a subclinical seizure sufficient to produce a non-specific arousal could also trigger a parasomnia.

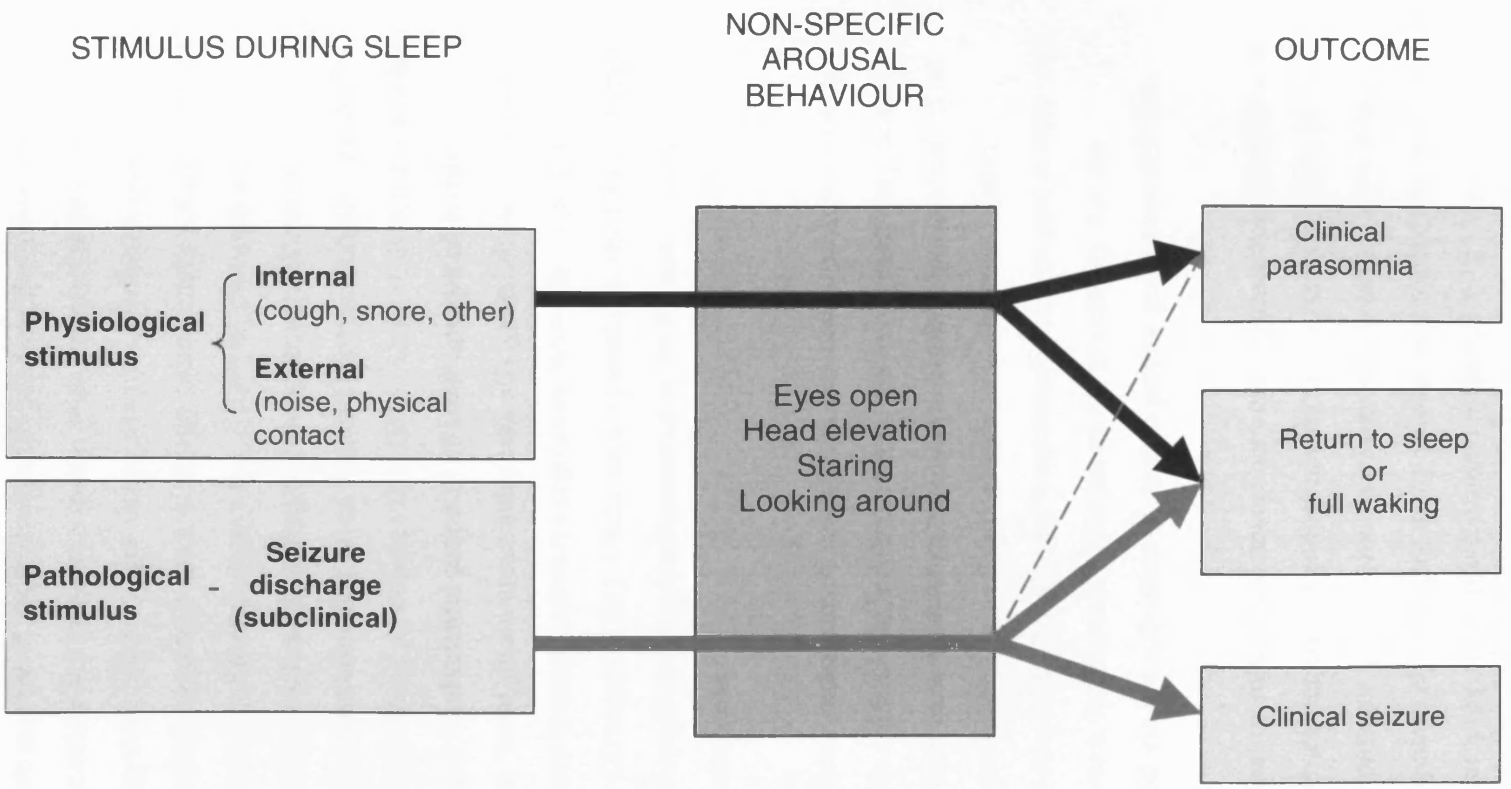


Figure 13. 4 *Schematic representation of the postulated relationship of arousal behaviour to parasomnias and nocturnal seizures. During sleep, physiological stimuli (external or internal) or subclinical seizure discharges can induce indistinguishable arousal behaviours. In parasomnia subjects, these may evolve (heavy black arrows) to a clinical parasomnia or terminate with return to sleep or full waking. In individuals with nocturnal epilepsy (heavy grey arrows), clinically evident seizures with distinguishing characteristic behaviours and marked stereotypy may occur, or the event may terminate with full waking or return to sleep.*

Secondly, the EEG findings observed in this study, as in the studies of Gastaut and Broughton (Gastaut, 1965), support the concept of dissociated sleep in parasomnias. About one quarter of individuals with parasomnias showed evidence of electrographic dissociation in at least one event, with a posterior dominant alpha rhythm coexisting with anterior light sleep patterns. While the precise biological foundation of this pattern is unclear, it appears to imply a state in which regions of the brain (including frontal, temporal and parietal cortices) are functionally asleep, but other areas (including the thalamocortical circuits involved in generating the posterior dominant rhythm) are functionally "awake". This is consistent with the emerging concept that sleep, rather than being a whole-brain property, is in fact a fundamental property of small groups of highly interconnected neurons; 'local' brain areas independently generate sleep patterns, and are then synchronised through extensive regulatory networks to produce global sleep behaviour (Krueger, 2002). Using such a paradigm, the EEG patterns suggest that a failure of synchronising mechanisms may be fundamental to the pathophysiology of parasomnias.

Thirdly, a relatively narrow repertoire of behaviours was observed in parasomnias; this finding may provide clues to the mechanisms involved in generating complex behaviour in a brain which is, at least in terms of cortical function, 'asleep'. The three patterns of behaviour seen (arousal behaviours, non-distressed motor activity, and distressed emotional behaviour) were broadly stereotyped within, and to a certain extent between, individuals. This raises the possibility that the behaviours are mediated via the activation of central pattern generators (CPGs).

CPGs are primitive spinal or subcortical neural networks, definitively identified in a number of animals, which are able to endogenously (i.e. without sensory or cortical input) produce patterns of behaviour (Grillner and Wallen, 1985; Hooper, 2000). They are phylogenetically ancient; many studies of these systems have been conducted in the lamprey, a primitive lizard (Grillner, 2003). There is, however, considerable evidence that similar mechanism operate in higher animals including mammals, although the large number of cells in the mammalian central nervous system makes it more difficult to identify these networks using standard electrophysiological and anatomical techniques (Grillner, 2003; Kiehn, 2006).

CPGs range from the very basic, for example those coordinating protective reflexes (such as coughing) or rhythmic respiratory patterns, to more complex patterns involved in locomotion. While some are continuously active (such those producing respiration) others (such as those involved in locomotion) can be turned on and off - in mammals the latter are largely under neocortical control (Grillner, 2003; Tassinari et al., 2005). Although most work on CPGs has examined their role in relatively simple repetitive behaviours such as locomotion, there is also evidence that they encode more complex innate behaviours. "Sham rage" was first described by Bard in 1928 (Bard, 1928). This term describes apparently angry behaviours in cats in which both cerebral hemispheres had been removed. In response to minimal external stimulation they would snarl, back arch and lash their tails; hypertension, tachycardia, piloerection and pupillary dilation were also observed. The presence of such behaviour in the absence of a cerebral cortex suggests that such innate emotional behaviours are coded in subcortical networks; from this finding in cats it is reasonable to hypothesise that emotional behaviours are encoded in a similar manner in other animal species, including humans (Grillner, 2003).

A possible role for CPGs in NREM arousal parasomnias has previously been suggested by some authors (Mahowald, 2002; Tassinari et al., 2005), but the lack of detailed video EEG evidence has made definite conclusions difficult. The finding of three main behavioural patterns in the current study, however, provides support for such a hypothesis; it is plausible that these patterns seen largely reflect innate CPG encoded behaviours which are triggered inappropriately during NREM sleep in these individuals. If this is this case, by what mechanism might this occur? The expression of many CPGs is thought to be predominantly under neocortical control during wakefulness, with the circuits inactive at rest but with the capacity to 'turned on' by cortical command centres (Grillner, 2003). During normal NREM sleep, there is reduced metabolic activity and cerebral blood flow in large areas of cerebral cortex (see literature review Chapter 3, pages 79-80, for further details), such that these CPGs are rarely activated. In a NREM arousal parasomnia, however, it is possible that disordered arousal is sufficient to activate subcortical CPGs but insufficient to produce normal waking cortical function. The only reported functional imaging study peformed during a NREM arousal

parasomnia supports such a mechanism, demonstrating relative hypoperfusion in neocortical regions with relatively increased blood flow in thalamic and cingulate regions (Bassetti et al., 2000). In parasomnias, therefore, CPG-encoded emotional, ambulatory or simple arousal behaviours may be expressed in an unrestricted fashion during apparent sleep, without cortical control. Apparently purposeful behaviours are thus simply the reflection of such uninhibited CPG activity, and the emotional distress observed is analogous to the "sham rage" of decorticate cats (Mahowald, 2002).

Evolutionary considerations arising from animal studies in sleep add an additional perspective to a discussion of CPGs and parasomnias. Mammals and birds, which diverged from a common reptilian ancestor over 310 million years ago, have been widely studied and every species exhibits sleep, including both NREM and REM sleep (Rattenborg, 2002). However, sleep is much more difficult to study in reptiles; these animals have no neocortex, and their EEG patterns are entirely unlike those of birds and mammals. As such, interpreting sleep-wake state is problematic, and even defining sleep (as opposed to inactivity) is not straightforward. Although some understandable inconsistencies therefore exist in descriptions of reptilian EEG, a number of studies report diffuse slow activity in the delta frequency range in the active reptile, and low amplitude, largely featureless EEG during apparent sleep (Nicolau et al., 2000). Moreover, spindles with a very similar appearance to human sleep spindles have been reported during periods of physical activity these animals (Gaztelu et al., 1991; Nicolau et al., 2000). Taken together, these findings have led to an interesting evolutionary hypothesis of sleep. The concept of "advanced wakefulness" proposes that REM sleep in mammals is analogous to the resting or 'asleep' state in reptiles (Rial et al., 1993; Nicolau et al., 2000); the loss of endothermic control in REM sleep, as well as EEG patterns in reptilian sleep, is consistent with this idea. NREM sleep, with delta activity and sleep spindles, is considered analogous to reptilian wakefulness, and mammalian (or "advanced") wakefulness is considered to be the most recent evolutionary adaptation. The radical concept in this theory is that NREM and REM sleep, rather than being evolutionary developments with specific adaptive functions, actually remnants from a more primitive phylogenetic era. These sleep states may have acquired new functions over time, such as a role in

the consolidation of memory, although specific functions of sleep remain to be definitively identified. Nevertheless, if such functions exist, they may have evolved from the pre-existing 'structures' of reptilllian activity and rest – such evolution of function is widespread in nature, for example the development of the jaw in land-based animals from the branchial arches of fish and amphibians (Nicolau et al., 2000).

How are such considerations relevant in terms of parasomnias? If NREM sleep is the evolutionary equivalent of an active state in reptiles, it is reasonable that primitive motor patterns such as searching behaviours and expressions of fear are capable of being expressed during this state; as previously discussed, such behaviours are likely to be encoded in subcortical CPGs. In normal sleep such behaviours occur infrequently, probably because profound thalamic functional deafferentation and relative neocortical cortical inactivity prevent their stimulation; in other words, CPGs are not 'switched on'. If, however, a disordered arousal in NREM sleep activates the primitive CPG-encoded behaviours without producing normal mammalian "advanced wakefulness", the individual will engaging in simple behaviours involving primitive cerebral structures, without cortical involvement. Their environmental interaction and behavioural responses can be considered, in a sense, 'reptilian'.

E. Theoretical considerations – parasomnias, NFLE and CPGs

Many automatisms have been described in epileptic seizures, some with lateralising or localising value (Loddenkemper and Kotagal, 2005). It has occasionally been hypothesised that CPGs may play a role in epileptic automatisms; oral automatisms in temporal lobe epilepsy may reflect feeding-related CPGs, and the bipedal automatisms of frontal lobe epilepsy may reflect activation of locomotor CPGs (Meletti et al., 2004; Tassinari et al., 2005). Tassinari and colleagues have advanced this concept, and recently suggested that the same mechanism may be responsible for the behaviours in parasomnias, although they acknowledge a lack of video EEG monitoring data to support such a hypothesis (Tassinari et al., 2005). These authors cite McLean's concept of the "triune brain" (MacLean, 1990), an evolutionary concept which has similarities to

the theory of "advanced wakefulness" discussed previously; in this model the human brain is comprised of three evolutionary strata, each based upon the layer before it. The "reptilian" brain is the most phylogenetically ancient, with the "paleomammalian" and "neomammalian" brains being more recent evolutionary additions. The authors suggest that fundamental behaviour patterns, encoded in CPGs in primitive 'reptillian' brain structures, are expressed in parasomnias and epileptic automatisms.

The finding of several broadly stereotyped categories of behaviour in this study supports a potential role for CPGs in parasomnias. However, if these networks are involved in both epileptic seizures and parasomnias, why are there clear qualitative and quantitative differences in the behaviour patterns observed? The case for CPG involvement in parasomnias has already been made; likewise, the repetitive and highly stereotyped automatisms seen in seizures of NFLE make it highly likely that such a mechanism is involved in this condition. It is possible, however, that the pattern of CPG activation differs in the two conditions. During a frontal lobe seizure, subcortical structures including the basal ganglia (which appear to play an important role in the regulation of CPG's (Grillner, 2003)), are repetitively stimulated in an abnormal, non-physiological, manner. As a result, bizarre, automatisms which may comprise fragments of other normal behaviours encoded in this fashion (such as bicycling) are expressed; these have an unusually explosive, repetitive, frenetic and minimally interactive quality. In contrast, the abnormal arousal of parasomnias may result from a more physiologically 'normal' stimulation of these behaviour patterns; the abnormality in this situation is not so much the manner of stimulation of these neural circuits, but rather the fact that this stimulation is occurring in the context of impaired neocortical function consistent with a NREM sleep state.

A striking, and related, finding in this study was the marked similarity between parasomnias and the *post-ictal* behaviours observed in NFLE. Eye opening, looking around, searching behaviours, semipurposeful fumbling with objects and partial verbal interaction with individuals in attendance were common both postictally and during parasomnias, and were qualitatively almost identical. Two other recognised postictal behaviours were also prominent in the parasomnia

group. Firstly, prominent and often vigorous nose or face wiping, a widely reported and often lateralising postictal behaviour in temporal lobe epilepsy (Hirsch et al., 1998; Geyer et al., 1999; Meletti et al., 2003), was frequently observed in parasomnias; this behaviour was seen infrequently in the NFLE comparison group, in line with previous studies of this phenomenon (Geyer et al., 1999; Catenoix et al., 2004). Secondly, some individuals in the parasomnia series reacted in a resistive or aggressive fashion to comforting or restraint, behaviour which were not seen if the subject was left alone; this observation is concordant with the clinical experience that attempts to restrain individuals during sleep terrors or sleepwalking can lead to resistance and occasionally violence (Plazzi et al., 2005). Although the aggression observed on video EEG monitoring in this study was mild, it was qualitatively similar to the non-directed, "reactive" or "affective" aggression which may occasionally be seen postictally in epilepsy patients. Such postictal aggression appears to particularly be seen in individuals with frontal and temporal lobe epilepsy, and usually arises in response to restraint (Gerard et al., 1998; Tassinari et al, 2005). It is possible, therefore, to speculate that the physiological conditions in parasomnias and the postictal state (particularly in NFLE) are similar. While seizures in NFLE usually terminate in full wakefulness, a brief period of postictal behaviour is often observed, which presumably results from dysfunction in the epileptogenic cortical networks. The postictal behaviour is, therefore, occurring in the context of diffuse cortical dysfunction in an otherwise 'awake' brain. This state may be functionally analogous to that of parasomnias; in both conditions there are active, 'awake', brainstem and diencephalic structures, but functionally inhibited neocortex. Quasi-physiological stimulation of CPGs without neocortical regulation may occur as in parasomnias, thereby producing similar behaviours. The SPECT study performed during a NREM arousal parasomnia, discussed previously, also provides some support for this concept. This demonstrated relative reduction in cerebral blood flow in large areas of frontal and parietal association cortex consistent with NREM sleep, but increased blood flow (more consistent with wakefulness) in thalamus and cingulate cortex (Bassetti et al., 2000). While consistent with sleep-wake state dissociation between diencephalic structures and neocortex, this pattern is also comparable to that seen in SPECT studies of focal epilepsy (including FLE) in which there is a post-ictal reduction in blood flow in

the area of seizure activity but relatively preserved blood flow elsewhere (Newton et al., 1992, 1995).

CHAPTER 14

SEVERE ADNFLE WITHOUT A KNOWN NICOTINIC ACETYLCHOLINE RECEPTOR MUTATION

Introduction

Autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE) is a familial partial epilepsy syndrome characterized by frontal lobe motor seizures occurring predominantly during light sleep. To date, ADNFLE has been associated with seven mutations in the genes encoding the α4 and β2 subunits of the neuronal nicotinic acetylcholine receptor (nAChR). Four are in CHRNA4, the gene coding for the neuronal nicotinic acetylcholine receptor (three missense mutations, Ser248Phe, Ser252Leu, and Thr265Ile (Steinlein et al., 1995; Hirose et al., 1999; Leniger et al., 2003); and one insertion, 776ins3 (Steinlein et al., 1997)); and three missense mutations (Val287Leu, Val287Met, Ile312Met) have been identified in CHRNB2, the gene coding for the neuronal nicotinic acetylcholine receptor β2 subunit (De Fusco et al., 2000; Phillips et al., 2001; Bertrand et al., 2005). These recognized mutations account for only a minority of families with the condition (Combi et al., 2004). Recently, however, evidence of alternative molecular defects in ADNFLE has started to emerge. Two nucleotide variations in the promoter region of the corticotrophin-releasing hormone (CRH) gene have been identified which are hypothesized to play a role in the pathogenesis of ADNFLE (Combi et al., 2005), although the significance of this finding is not yet clear. Finally, a mutation of the gene coding for the α2 subunit of the nAChR was reported in a single large family with ADNFLE (Aridon, 2006).

Clinical descriptions of ADNFLE indicate that seizure control may be variable during childhood but often improves in adulthood, with seizures typically responsive to carbamazepine (Scheffer et al., 1995). Within families there is substantial variability in the severity of this condition (Scheffer et al., 1994); while some individuals may have severe epilepsy, a substantial proportion are often only mildly affected, being fully controlled on a single antiepileptic drug or never seeking medical attention (Scheffer et al., 1995; Phillips et al., 2001). While

seizures may be very frequent in ADNFLE, status epilepticus is rare. Affected individuals are typically of normal intelligence, although two families with ADNFLE associated with mental retardation have been reported (Khatami et al., 1998; Cho et al., 2003). Psychiatric and behavioural morbidity has occasionally been reported in ADNFLE, but has largely been regarded as a misdiagnosis of the seizures themselves (for example as hysteria or psychogenic non-epileptic seizures) due to the unusual seizure semiology and normal investigation findings (Scheffer et al., 1994; Magnusson et al., 2003). Alternatively, psychiatric features have been conceptualized as a consequence of delayed diagnosis of epilepsy, or attributed to the impact of chronic illness (McLellan et al., 2003).

Here, two families with ADNFLE are described in whom a number of atypical cognitive, behavioural, and psychiatric features were seen, often in association with frequent refractory seizures and episodes of status epilepticus. Neither family carries a mutation in the nicotinic acetylcholine receptor subunit genes. These families, while still within the spectrum of ADNFLE, represent a more severe phenotype than that usually described in this condition.

Subjects and Methods

Clinical information on two unrelated, non-consanguinous families containing 17 affected individuals from Australia and the UK was obtained. Available living affected family members underwent detailed assessment. I assessed all affected members of both families, and collected blood samples, on at least two separate occasions. Assessments comprised clinical interviews (including a validated seizure questionnaire (Reutens et al., 1992) and physical examination) in affected and unaffected individuals, correspondence with professionals involved with their clinical management, and review of medical records and investigations, including EEG, video-EEG monitoring and neuroimaging. Extensive pedigrees were constructed and genetic analysis performed. 'Mental retardation' and 'behavioural disorder' in this study were defined according to the criteria for Mental Retardation and Attention-Deficit and Disruptive Behaviors in DSM-IV-TR (Association, 2000). Some members of Family A were reported in the original description of ADNFLE (Scheffer et al., 1994); Family B has not been previously

reported. Previous study of the Family A pedigree also provided evidence of linkage to 15q24 (Scheffer et al., 1994; Phillips et al., 1998), but phenotyping was incomplete. The family has now been further expanded with detailed phenotyping undertaken in all individuals.

Molecular Genetics

Molecular genetic analysis was conducted by Ms S. Heron and A/Prof J. Mulley at the Department of genetic medicine, Women's and Children's Hospital, Adelaide, Australia. I was not directly involved in this analysis.

Genotyping

PCR amplification was carried out on genomic DNA using ^{32}P dCTP as previously described (Phillips et al., 1995; Phillips et al., 1998). A genome-wide search was performed using highly polymorphic microsatellite markers, chosen primarily from the Généthon maps (Weissenbach et al., 1992; Gyapay et al., 1994). Fine mapping was performed for chromosome 15q, 20q and 1q.

Linkage analysis

LOD scores, between ADNFLE and 15q and 1q markers, were calculated using MLINK. The analysis assumed autosomal dominant inheritance with 75% penetrance, and an affected allele frequency of 0.0001. Only affected family members and obligate carriers were included in linkage analysis, both in excluding linkage (through evidence of recombination) and in demonstrating linkage through LOD-score analysis, as ADNFLE is associated with incomplete (approximately 75-80%) penetrance (Oldani et al., 1998). Observations of recombination between ADNFLE and intragenic *CHRNA4* and markers were used to exclude linkage between ADNFLE and these regions. These intragenic polymorphisms have been described previously (Steinlein, 1995; Weiland and Steinlein, 1996; Phillips and Mulley, 1997).

Mutation Analysis

Mutation analysis for known mutations in *CHRNA4* and *CHRNAB2* was performed by single strand conformation analysis (SSCA) and direct DNA

sequencing, using previously published primers (Phillips et al., 1998; Phillips et al., 2001). These genes were also screened for new mutations using SSCA.

Results

Family A is from the UK and family B from Australia. The two families are unrelated and non-consanguinous. Pedigrees showing the distribution of epilepsy, psychiatric and cognitive disorders are displayed in Figure 14.1, and the phenotypic features of the 17 affected individuals are shown in Table 14.1. Age of onset was relatively early (mean 7.8 years, median 7 years). Overall seizure frequency during periods of poor control was high (mean 33 seizures per night, median 30), and status epilepticus was seen in four cases (two from each family, 24%). Individuals with an earlier age of onset tended to have more severe epilepsy; those with onset at seven years or younger reported a median of 40 seizures per night compared to a median of 20 per night in those with a later onset, although this difference was not statistically significant. 9 individuals (53%) had seizures during wakefulness, coinciding with periods of poor control; in 3 individuals, unusual daytime events with an 'atonic' semiology were also seen (described in the case reports below).

Nine individuals (53%) gave a history of a psychiatric or behavioural disorder, requiring at least one psychiatric admission in four cases (24%). In childhood, behavioural disturbance took a variety of forms. In some individuals it was predominantly aggressive, hostile and destructive behaviour; in others, running away, distractibility and overactivity were the most marked traits. In adulthood, the most frequent psychiatric diagnosis was depression (diagnosed in three individuals); in one case this may have been associated with psychotic features, but medical records from the time are no longer available. Two individuals have a personality disorder and one has been diagnosed with paranoid schizophrenia. Mental retardation (MR) was seen in four affected individuals (24%), with two individuals (one from each family) showing developmental regression in association with periods of poor seizure control or status epilepticus; in the more severe case, regression was from an active and normally developing four year old

to a fully dependent, wheelchair bound and markedly bradyphrenic, almost mute, adult. In the four individuals with MR, three have mild to moderate MR and one has moderate to severe MR. No psychiatric or cognitive disorders were reported in the unaffected members of these families.

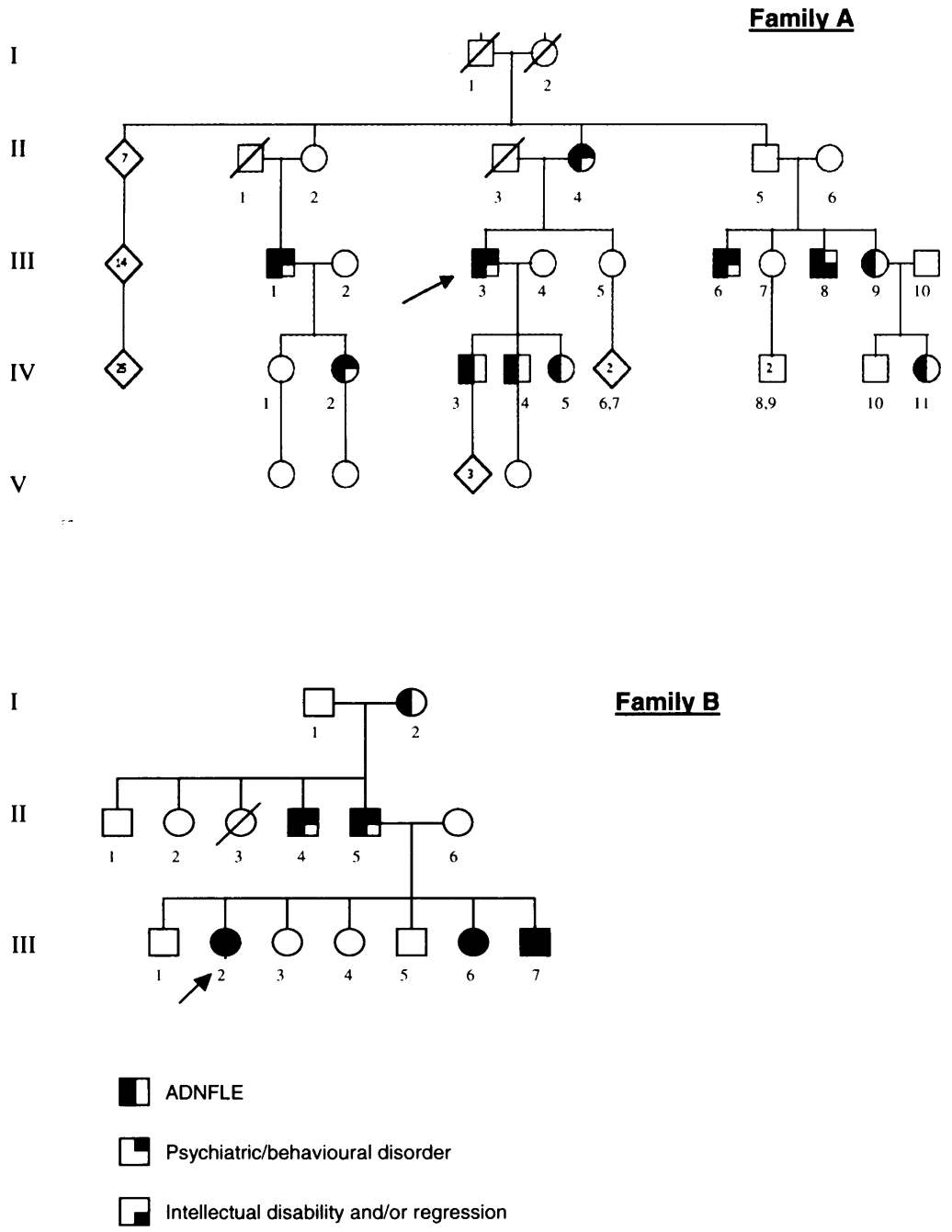


Figure 14. 1. *Family pedigrees showing the distribution of ADNFLE, behavioural/ psychiatric disorders, and intellectual disability.*

Family and Pedigree Reference	Age at Onset	Age at interview	Seizure types		Refractory epilepsy at time of interview	Reported seizures per night*	Status epilepticus	Behavioural or psychiatric disorder	Mental retardation	Develp-mental regression	Neurological abnormalities
			Nocturnal	Diurnal							
A II-4	10	76	partial	-	-	40-80	-	depression †	-	-	-
A III-1	17	63	partial, rare GTC	-	Yes	20	-	depression	-	-	-
A IV-2	13	33	partial	-	-	Up to 40	-	depression	-	-	-
A III-3	7	57	partial, rare GTC	-	Yes	40+	yes	Behavioural disorder†	-	-	-
A IV-4	10	33	Partial	partial	-	10	-	-	-	-	-
A IV-3	7	37	Partial	partial	-	20	-	-	-	-	-
A IV-5	7	21	Partial	partial	-	40	-	-	-	-	-
A III-6	14	51	Partial, GTC	partial	-	12	-	Paranoid schizophrenia†	-	-	-
A III-8	4	45	Partial, ?GTC	partial	Yes	100+	yes	-	yes	yes	yes (hemiparesis, extrapyramidal signs, ataxia)
A III-9	4	36	partial	partial	Yes	5	-	-	-	-	-
A IV-11	9	14	partial	partial	Yes	40	-	-	-	-	-
B I-2	Not known		partial	-	-	infrequent	-	-	-	-	-
B II-4	2	33	partial	-	-	50	-	Personality disorder	-	-	-
B II-5	15	45	partial, rare GTC	-	Yes	20	-	Depression	-	-	-
B III-2	3	21	partial	partial	Yes	40-60	yes	Personality disorder†	yes	yes	-
B III-6	2	6	partial	partial	Yes	12	yes	Behavioural disorder	yes	-	-
B III-7	1	5	partial	-	Yes	6	-	Behavioural disorder	yes	-	-

Table 14. 1. *Summary of the clinical features of families A and B.*

*This frequency often changes throughout an individual's lifetime; numbers quoted reflect periods when the disorder was most active, usually in childhood and adolescence.

†Indicates at least one hospital admission for psychiatric or behavioural disorders

Case histories

Subject A III-8. This 44 year old man was the product of a normal pregnancy and had normal early development. At four years, following a single daytime febrile convulsion in the context of an upper respiratory tract infection, he developed frequent nocturnal seizures characterized by screaming, dystonic posturing and violent thrashing. Epilepsy was very severe from the onset, with 6 to 200 seizures every night, exclusively during sleep and without apparent aura or retained awareness. Rare secondarily generalized tonic-clonic seizures also occurred. The onset of seizures was associated with a rapid and dramatic loss of motor skills with loss of walking and running and he could only crawl with difficulty. No deterioration in speech or cognition was noted. He was seizure free for four months on phenytoin and phenobarbitone and slowly regained motor skills, including crawling and eventually walking, although these never returned to normal. One year after seizure onset, he had an episode of probable tonic-clonic status epilepticus and was left with a mild right hemiparesis. His written and verbal language skills remained within the normal range. However, frequent (10-15) nightly seizures continued and in teenage years he began to struggle at school, particularly in mathematics.

At 15 years, a further episode of probable tonic-clonic status epilepticus requiring intensive care admission occurred in the context of diabetic ketoacidosis which was the first presentation of type 1 diabetes mellitus. Cognitive and motor decline followed, with significant loss of written and verbal language skills and worsening of his hemiparesis, such that he was unable to walk unaided and was no longer able to attend school. Seizures continued on a nightly basis throughout his life despite numerous anticonvulsants; in recent years, identical daytime seizures have occurred. Periods of poor seizure control during his adult life have corresponded with a progressive deterioration in motor and cognitive function. He is now markedly bradyphrenic, and speaks only a few words. He is unable to walk unaided and is fully dependent on assistance for all activities of daily living. On neurological examination he has diffusely increased tone in an extrapyramidal pattern, a right hemiparesis and mild trunkal ataxia. Interictal EEGs demonstrated diffuse slowing but no epileptiform activity. CT brain scan at age 40 showed

atrophic changes, primarily in the cerebellum with bilateral frontal cortical atrophy, and no other focal lesions.

Subject A III-6. This 51 year old man was the product of a normal pregnancy, with normal development. At 14 years, he developed episodes 'like butterflies in the stomach' during waking hours, but without impaired awareness or motor features. At 16 he developed nocturnal seizures characterized by an abdominal sensation and breathlessness, followed by generalized tonic stiffening with retained awareness. These lasted for around 1 minute, with up to 12 nightly. Occasional nocturnal generalized tonic-clonic seizures and daytime partial seizures were also observed, usually in association with anticonvulsant omission. Ambulatory EEG monitoring (4 channels only) recorded two events in which a clear ictal rhythm of rhythmic sharp theta activity, maximal over the left hemisphere, was observed. CT brain was normal. Seizures were refractory to multiple medications until 40 years.

With the onset of nocturnal seizures his personality and behaviour deteriorated abruptly, and he changed from a quiet to an aggressive and temperamental adolescent. He was frequently involved in arguments and fights, and was arrested on several occasions. He was made redundant from his electrician apprenticeship after less than 1 year and has not worked again. He increasingly abused alcohol and became socially isolated. In his 20's, he took numerous non life-threatening overdoses of antiepileptic drugs. In his 30's, he had two unprovoked episodes of psychosis, the second requiring a six month inpatient admission when a diagnosis of paranoid schizophrenia was made. These episodes were unrelated to seizure activity as his seizures were becoming increasingly infrequent. By 40 years, he was seizure-free on carbamazepine monotherapy, but remains on long-term antipsychotic medication to manage fluctuating psychotic delusions.

Subject B III-6: This 6-year-old girl was the product of a normal pregnancy and delivery. Motor development was normal but language was delayed; she had single words by one year but did not put two words together until 2½ years of age. Now, at 6 years, her language is at a 3-year-old level. She rarely speaks in sentences, but continues to make gains and no regression has been noted.

Seizures, characterized by sudden repetitive limb thrashing, began at 2 years 9 months of age, occurring twelve times per night. Interictal EEGs and MRI brain were normal, but typical frontal lobe seizures were recorded on video EEG monitoring, associated with diffuse EEG attenuation. Ictal SPECT demonstrated hyperperfusion of the right superior frontal gyrus. Her epilepsy remains severe and refractory to treatment with numerous antiepileptic drugs.

She has had very severe behavioural problems since from the onset of epilepsy, being described by her parents as 'uncontrollable'. She is overactive, distractible and prone to severe tantrums, and lacks appreciation of normal social cues. She has a tendency to 'run away' to the point where her parents and teachers must ensure doors are locked at all times.

Recently she had 3 episodes of focal frontal lobe status epilepticus in a 1 month period; this worsening in seizure control was associated with significant behavioural deterioration. She has also recently developed occasional daytime seizures with an atonic component. During these episodes, which occur at any time of day and are not associated with an apparent aura, she suddenly becomes limp 'like a rag doll'. Her head and body tend to fall to the right, her eyes roll and she is unresponsive for up to a minute. If standing she will collapse, and has sustained some minor head injuries. Postictally she makes a rapid recovery, although may walk with a limp for two hours.

Subject B III-2. This 21 year-old-woman was the product of a normal pregnancy, with normal early development. She was a well behaved child, although she 'never knew how to play' like her siblings, and was socially 'over friendly'. Seizures began at 3 years, occurring up to sixty times per night, with yelling out, gasping and prominent dystonia. Video EEG monitoring recorded stereotyped hypermotor seizures associated with bifrontal fast activity. Two ictal SPECT studies demonstrated right orbitofrontal hyperperfusion. Serial MRI scans of the brain were normal.

Frequent nocturnal seizures continued throughout early childhood despite numerous antiepileptic drugs. She had recurrent episodes of focal status epilepticus, requiring hospitalization on six occasions prior to 10 years. At 5 years, following frontal status epilepticus, she lost motor, verbal and cognitive skills and was unable to sit up or walk at discharge. However, she fully regained these skills over two weeks. She struggled academically; an intellectual assessment using the Wechsler Preschool and Primary Scale of Intelligence at 6 years indicated mild intellectual disability.

She was seizure free between 10 and 11 years, but at 13 years with the onset of puberty, her seizure control deteriorated markedly. Sixty or more seizures occurred nightly, and this was associated with a sudden and severe decline in both her behaviour and cognitive function. She developed severe and rapid mood swings, with frequent violent and abusive outbursts in which she would smash objects, injure herself or threaten suicide. She was increasingly socially inappropriate, undressing in public or acting in a sexually inappropriate manner with males. Language and cognitive skills deteriorated, and she became incontinent of faeces and urine during both day and night. At age 14, she scored 45 on IQ testing (using WISC-III), placing her in the moderate MR range. She could no longer be managed at home, and was placed in institutional care. She has subsequently required admission to inpatient psychiatric services on 10 occasions over the last 11 years, and has been diagnosed with a complex range of neurodevelopmental problems comprising an emerging personality disorder, anxiety, and depression with a rapidly cycling and episodic nature. Her behaviour has partially responded to treatment with citalopram and counseling but remains a significant problem. Further neuropsychological reviews have continued to place her in the moderate MR range. Seizures occur nightly, despite multiple antiepileptic drugs, and she now has daytime seizures occurring around 5 days per month; although these are usually identical to her nocturnal events, occasionally she will have "atonic" events similar to those of her sister (described above).

Molecular genetics

Family A

CHRNA4. Affected individual A IV-2 did not inherit a copy of *CHRNA4* from her carrier grandmother, excluding linkage to this gene .

CNRNB2. Segregation of ADNFLE with haplotype markers for a 6.6 cM region on chromosome 1q21 between markers D1S2343 and D1S2715; this region contains *CNRNB2*. Co-segregration of haplotypes is shown in Figure 14.2, LOD scores are given in Table 14.2. However, the maximum LOD score was not significant (LOD score 1.66 at a recombination factor of 0); the informative marker was D1S2715. Two individuals were sequenced for the coding exons of *CNRNB2* and no mutations were detected. No intragenic coding SNP was detected in the family.

Chromosome 15q24. Family A also showed evidence of linkage to Chromosome 15q24 as previously reported (Phillips et al., 1998). Regional localization was between markers D15S211 and D15S152. Co-segregration of haplotypes is shown in figure 14.3; LOD scores are shown in Table 14.3. Previously, the region was thought to include the cholinergic subunit genes *CHRNA3, CHRNA5,* and *CHRNB4* (18), but the use of closely spaced Généthon markers showed that these genes were *ouside* the region.

Family B

CHRNA4. Using intragenic markers, linkage of family B to *CHRNA4* cannot be excluded but one family member has been sequenced for exons 1-6 of *CHRNA4* and no mutations were identified.

CNRNB2. Linkage of family B to *CHRNB2* was excluded through evidence of recombination in the region of 1q21 involving this gene.

Chromosome 15q24. Linkage of family B to 15q24 was excluded through analysis of haplotype markers.

Figures of family B haplotype markers for chromosomes 1q21 and 15q24, as well as for the AC triplet repeat marker in *CHRNA4*, are shown in Appendix B.

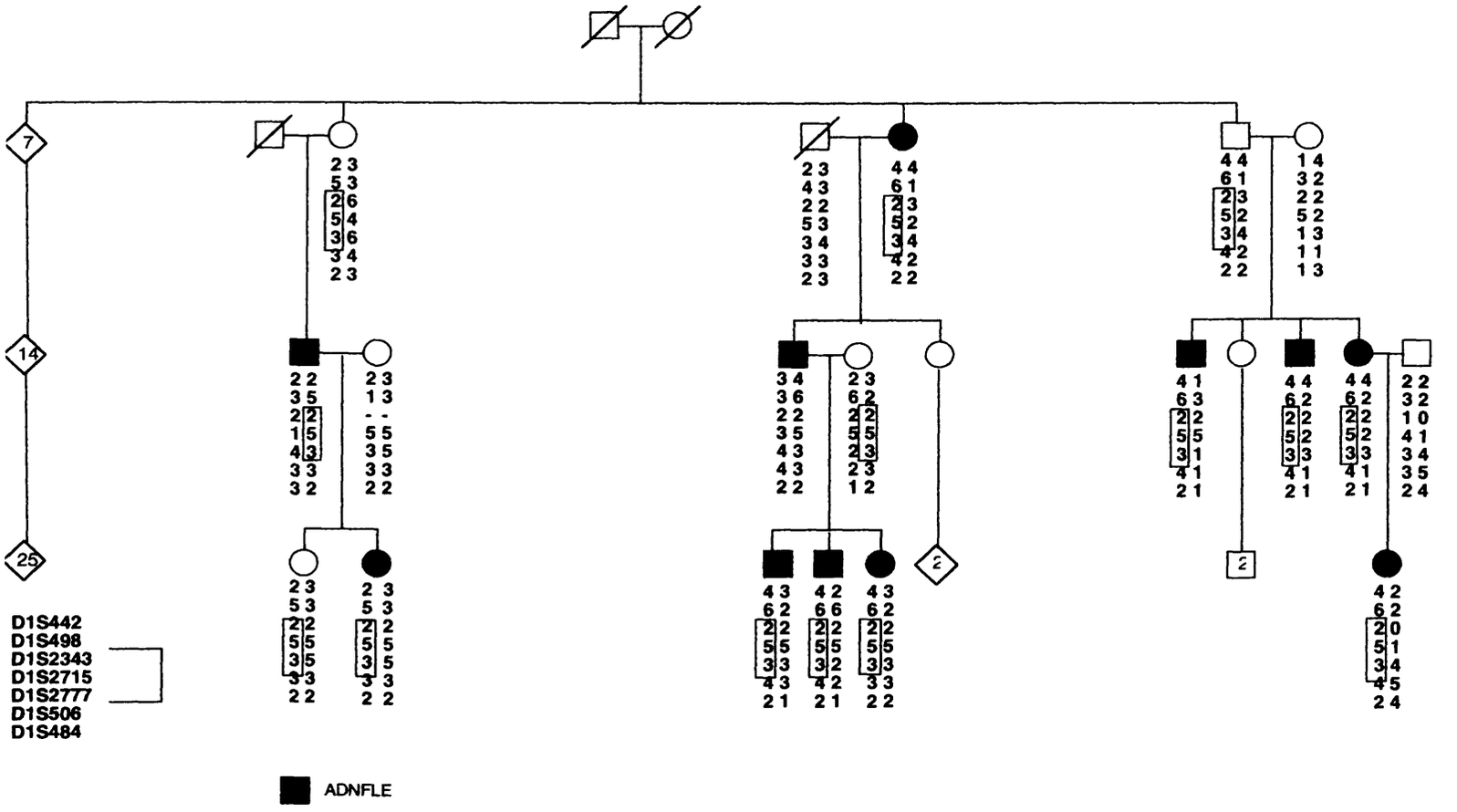


Figure 14. 2. *Segregation of haplotype markers for chromosome 1q21 with ADNFLE in Family A. All affected individuals, obligate carriers, and unaffected parents of affectd ind ividuals are genotyped.*

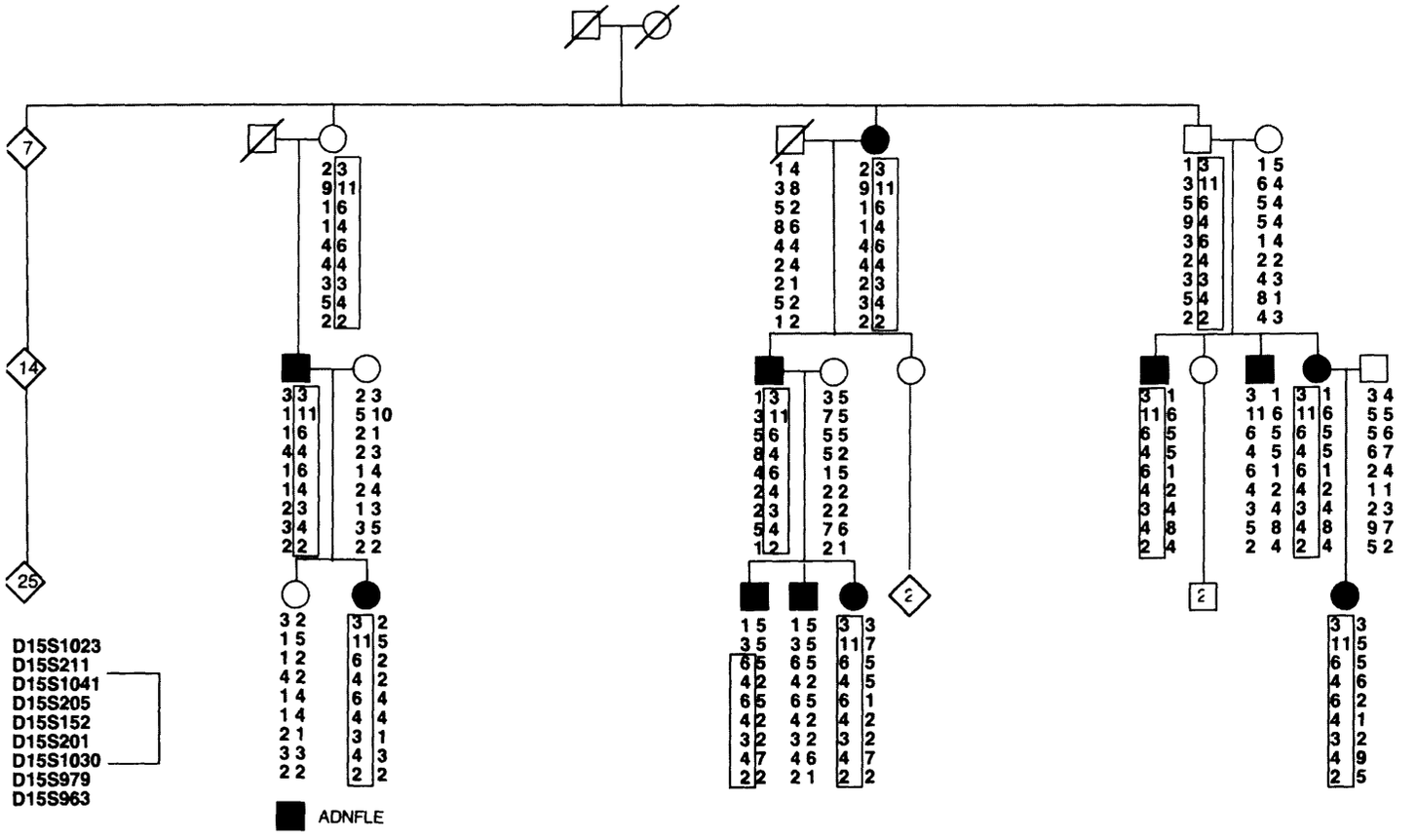


Figure 14. 3. *Segregation of haplotype markers for chromosome 15q24 with ADNFLE in Family A. All affected individuals, obligate carriers, and unaffected parents of affectd ind ividuals are genotyped.*

Marker	LOD score at recombination fraction (θ) of:						
	0.0	0.01	0.05	0.1	0.2	0.3	0.4
D1S442	-2.18	-0.68	-0.03	0.21	0.36	0.34	0.21
D1S498	-1.49	0.40	0.98	1.12	1.05	0.76	0.38
D1S2343	0.98	0.96	0.89	0.79	0.56	0.31	0.09
D1S2715	1.66	1.64	1.53	1.39	1.05	0.68	0.32
D1S2777	1.34	1.32	1.23	1.11	0.81	0.46	0.14
D1S2506	-5.59	-1.42	0.17	0.25	0.45	0.36	0.18
D1S484	0.34	0.34	0.32	0.30	0.26	0.19	0.11

Table 14. 2. *Two-point LOD scores for chromosome 1q21 markers in Family A.*

Marker	LOD score at recombination fraction (θ) of:						
	0.0	0.01	0.05	0.1	0.2	0.3	0.4
D15S1023	-1.96	-1.51	-0.40	0.04	0.30	0.26	0.10
D15S211	-1.46	-1.02	0.07	0.47	0.64	0.51	0.24
D15S1041	2.72	2.67	2.48	2.22	1.64	1.00	0.40
D15S205	3.21	3.16	2.93	2.63	1.98	1.27	0.53
D15S152	2.99	2.94	2.75	2.49	1.91	1.27	0.59
D15S201	2.72	2.68	2.50	2.26	1.73	1.13	0.53
D15S1030	1.85	1.81	1.68	1.52	1.20	0.85	0.45
D15S979	-0.98	1.28	1.78	1.82	1.53	1.05	0.50
D15S963	0.85	0.84	0.80	0.74	0.60	0.43	0.24

Table 14. 3. *Two-point LOD scores for chromosome 15q24 markers in Family A*

Discussion

Severe ADNFLE phenotype

Two families are presented with a severe form of ADNFLE, displaying a number of atypical cognitive and psychiatric features, in which no mutations of nicotinic acetylcholine receptor genes have been identified. Affected individuals in both families have more severe epilepsy with early onset, very frequent seizures, status epilepticus and high rates of intractability into adulthood. The mean age of onset in these families was 7.8 years (median 7 years) compared to the reported mean of 11.7 years (median 8 years)(Scheffer et al., 1995), and the overall seizure frequency per night (mean 33, median 30) is high compared to the reported frequency in ADNFLE (mean 7.7, median 6) (Scheffer et al., 1995). Status epilepticus is infrequently reported in ADNFLE, but was seen in one quarter of the affected individuals in these families. Half of the affected adults in these families are refractory to multiple AEDs, which is unusual in ADNFLE; while seizures in this condition often require lifelong treatment, they are usually easily controlled with carbamazepine. Also atypically for ADNFLE, in which marked intrafamilial variability in disease severity is usually seen (Scheffer et al., 1994; Oldani et al., 1998), all affected individuals in both families are severely affected with one exception; a single elderly woman in family B (B I-2) reported infrequent, minimally disruptive attacks, but she was very reluctant to discuss her epilepsy and the reliability of this history was uncertain.

Overall, while the clinical features in these families are consistent with the spectrum of ADNFLE, they appear to represent a more pernicious form than that usually reported; the epilepsy in the least severely affected individuals here is as severe as or worse than that of the more severely affected members of other ADNFLE families (Scheffer et al., 1995; Phillips et al., 2001). Moreover, a number of the most seriously affected individuals in these families have additional cognitive and affective comorbidities not usually seen in ADNFLE. Mental retardation, behavioural and psychiatric disorders are observed in individuals from both families, with definite developmental regression in two cases.

Mental retardation, regression, and psychiatric morbidity

Mental retardation (MR) is not usually associated with ADNFLE, although it has been previously reported in two families. In one of these, bilineal inheritance of MR and ADNFLE was observed, raising the possibility that these two features were segregating independently through the pedigree rather arising through a common mechanism (Khatami et al., 1998). More recently, however, a Korean kindred was described with ADNFLE and MR associated with the CHRNA4 Ser252Leu mutation (Cho et al., 2003); in this family, all individuals with epilepsy also had mild to moderate MR, and all but one had seizures persisting into adulthood despite treatment with multiple medication. MR and behavioural problems were also reported in some members of a Japanese family reported with the same mutation (Ito et al., 2000), and in a single member of a Norwegian family with the CHRNA4 Ser248Phe mutation (Steinlein et al., 2000). Overall, however, the majority of reports of ADNFLE emphasise normal intellectual function (Scheffer et al., 1995; Oldani et al., 1996; Nakken et al., 1999; Saenz et al., 1999).

While the majority of affected individuals in family A reported here have normal intellect, mild to moderate MR is a feature of half of the affected members of family B. Furthermore, in both families developmental regression was observed in individuals with very severe epilepsy; in the most severe example (A III-8), regression was from a normally developing and active 4 year old to a fully dependent, wheelchair bound and markedly bradyphrenic, almost mute, adult. Both individuals had frequent, refractory seizures with early clinical onset (4 years or younger), and regression was temporally related to episodes of focal frontal lobe or tonic-clonic status epilepticus. In one, regression was associated with the development of focal neurological deficits without neuroimaging correlate. To our knowledge, developmental regression has not previously been reported in ADNFLE.

The other striking feature in these families is the high incidence of behavioural and psychiatric disorders, ranging from depression to frank psychosis. Psychiatric diagnoses in individuals with ADNFLE were previously considered to be largely a

reflection of the burden of living with chronic, and often unrecognized, epilepsy; in some cases they represented direct misdiagnosis of the underlying condition as psychogenic nonepileptic seizures (Scheffer et al., 1994). Recently, however, this explanation has been questioned. Magnusson et al. proposed that the high rate of psychiatric diagnoses among patients with ADNFLE may not be an artifact, hypothesising that psychiatric disturbance is part of the clinical spectrum of ADNFLE associated with the CHRNA4 776ins3 mutation (Magnusson et al., 2003). A phenotypic comparison of two Scottish families with mutations in different genes causing ADNFLE (the Ser248Phe CHRNA4 and Val287Met CHRNB2 mutations) also noted significant rates of psychological morbidity in both families, with reports of depression, low self-esteem, a hysterical gait disorder and school refusal (McLellan et al., 2003). Although the mean delay of approximately 9 years between seizure onset and diagnosis in these families may have contributed to the psychiatric morbidity observed, the findings raise the possibility that mutations causing ADNFLE also directly predispose to mental illness.

The high rates of behavioural and psychiatric disorders in the families A and B reported here support this hypothesis. In many individuals these disorders are highly disabling, more so than the seizures themselves, and in 4 cases (24%) have resulted in affected individuals requiring institutional care. Although it is possible that some of this psychopathology is attributable to the burden of epilepsy, this is unlikely to fully explain the range and severity of problems observed. Significantly, ADNFLE was promptly recognized and treated in family B; despite this, five of the six affected individuals have significant psychiatric or behavioural disorders, indicating that missed or delayed diagnosis was not a significant factor in the development of psychopathology here.

Whether MR, regression, and behavioural and psychiatric disorders are a direct result of the genetic abnormality, a consequence of frequent frontal lobe seizures, or a combination of the two, is unclear. In contrast to the report of Magnusson et al (Magnusson et al., 2003), in which psychiatric features appeared despite good seizure control, psychopathology and developmental regression in families A and B usually developed in the context of frequent refractory seizures or frank focal

status epilepticus. It appears likely, therefore, that seizures play some role in the development of these comorbidities, even if they are not the sole cause. Such a hypothesis is biologically plausible. Cognitive and neurological sequelae have been reported following complex partial status epilepticus, albeit predominantly in status epilepticus of temporal lobe rather than frontal lobe origin (Krumholz et al., 1995), and affective or behavioural disturbance is well described during periods of ongoing focal frontal lobe status epilepticus (Thomas et al., 1999; Takaya et al., 2005). It has long been recognized that frontal lobe injury or dysfunction can result in a range of behavioural problems, including distractibility, poor attention, perseveration, disinhibition, irritability and aggression (Trimble, 1990). There is also considerable evidence of frontal lobe dysfunction in schizophrenia and depression (Weinberger, 1988; Trimble, 1990; Mayberg, 1994; Weinberger and Berman, 1996), with some clinical features of these conditions (such as including apathy, blunted affect, psychomotor retardation, and paucity of speech and spontaneous movement) being well-recognised features of frontal lobe dysfunction.

Taken together, these observations raise the possibility that the underlying genetic abnormality may confer a predisposition to such problems, but also that inadequate seizure control, with associated impairment of frontal lobe function, can precipitate a significant deterioration. This underscores the importance of prompt diagnosis and treatment in ADNFLE in order to minimize the development of these disabling features.

The role of the nAChR

ADNFLE has been definitively associated with mutations in genes coding for α4 and β2 subunits of the nicotinic acetylcholine receptor (nAChR); recently a mutation of the α2 subunit was also described (Aridon, 2006), suggesting that the α4β2 receptor may not be the only nAChR implicated in this disorder. Recognized mutations, however, account for only a minority of families with ADNFLE, and are not present in the families presented here.

Two possibilities arise from the molecular genetic findings in these families: either further, as yet unrecognized, nAChR mutations are responsible; or an alternative genetic basis to the disorder may exist. It remains possible, though unlikely, that the more severe phenotype presented results from novel mutations in nAChR genes. In family B, linkage analysis was able to exclude *CHRNB2* and the *CHRNA3/CHRNA5/CHRNB4* cluster, but not *CHRNA4*; however sequencing of this gene identified no mutations. In family A, *CHRNB2* may still be implicated as cosegregation of hapolotypes is consistent with linkage to 1q21, although sequencing of this gene has failed to identify a mutation. Linkage analysis has, however, excluded *CHRNA4* and the *CHRNA3/CHRNA5/CHRNB4*. The initial reported evidence for linkage to chromosome 15q from this family implicated a ≈ 6.3cM region, which appeared to include the *CHRNA3/CHRNA5/CHRNB4* gene cluster (Phillips et al., 1998). The region identified here through reanalysis with more affected individuals, more markers and better localization of markers *excludes* this cluster, indicating that these genes are not responsible for the ADNFLE phenotype in this family. As this is the only reported example of linkage to this region, any role for the *CHRNA3/CHRNA5/CHRNB4* cluster in ADNFLE must be questioned.

The sequencing of *CHRNB2* and *CHRNA4* in these families makes a mutation in these genes unlikely, but not impossible. Although DNA sequencing is extremely reliable for detecting nucleotide substitutions, it cannot always detect large deletions or duplications. A deletion might explain the more severe phenotype observed, as such mutations can have more profound consequences than nucleotide substitutions. A further possibility is a mutation in non-coding DNA, including promoter regions; these areas have occasionally been reported in familial diseases (Liu et al., 1999) but have not been sequenced in these families. Therefore although mutations in the nAChR genes previously implicated in ADNFLE are unlikely in these families, they cannot be firmly excluded.

Altered nAChR function is a biologically plausible mechanism for the comorbidities described here. The possible role of these receptors in mental illness has received increasing attention in recent years, stimulated by the substantially increased prevalence of smoking in schizophrenia (70-88%) (Hughes

et al., 1986; Leonard et al., 2001), ADHD (42%) (Pomerleau et al., 1995) and depression (46%) (Poirier et al., 2002) compared to the general population (28%). Smoking may represent self-medicating behaviour in these conditions, a possibility supported by reports of symptomatic improvements with nicotine administration (Dalack et al., 1998; Salin-Pascual and Drucker-Colin, 1998; Ripoll et al., 2004). In schizophrenia, evidence from post-mortem studies suggests reductions in CNS nAChR density, although more predominantly in α7 than α4β2 receptors (Freedman et al., 1995; Ripoll et al., 2004); this receptor appears to play an important role in auditory sensory gating, and dysfunction may be implicated in auditory hallucinations in this disorder (Ripoll et al., 2004).

Moreover, the nAChR (particularly the α4β2 receptor) also plays a critical role in synapse formation and modification of circuitry in the developing brain (Lipton and Kater, 1989; Pugh and Berg, 1994; Role and Berg, 1996). It is reasonable to hypothesise that dysfunctional nAChR in this setting could result in MR; reduced gene expression and post-transcriptional abnormalities of the α4β2 nAChR have recently been described in autism with MR (Perry et al., 2001; Lee et al., 2002; Martin-Ruiz et al., 2004).

Other genetic considerations

Although a mutation in a gene coding for one of the nAChR subunits may be responsible for the ADNFLE and associated features in these families, the molecular genetic analysis makes this relatively unlikely. The possibility is therefore raised of an alternative molecular mechanism, unrelated to the nAChR. This concept is supported by the recently published finding of two rare polymorphisms in the corticotrophin releasing hormone (CRH) promoter region in ADNFLE families with no nAChR mutation (Combi et al., 2005). However, this report is suggestive rather than conclusive; one of the polymorphisms was present in approximately 3.35% of normal controls, and the other, although not present in controls, was found in only one affected individual. Further studies are required before these polymorphisms can be conclusively established as a causative

molecular defect in ADNFLE, but the concept of a non-nAChR mutation in this condition is interesting.

Although family B presented here is too small for linkage studies, segregation of haplotypes in family A is potentially consistent with linkage to both 15q24 and 1q21. The LOD scores are significantly greater for the 15q24 locus than the 1q21, however (Tables 14.2 and 14.3), largely because the 1q21 markers are not highly polymorphic within Family A. As already discussed, the *CHRNB2* gene on 1q21 has been sequenced and no mutation identified, and the *CHRNA3/CHRNA5/CHRNB4* cluster on 15q24 has been excluded. A number of possible molecular mechanisms could explain these findings. Firstly, a non-nAChR gene on either chromosome 1q21 or 15q24 may carry the molecular defect in this family. Linkage as determined by the LOD score is a statistical inference. As with any statistical test, the possibility of false positives exists, and it is therefore likely that one of these two loci is correct and the other is irrelevant to the disorder. In addition to *CHRNB2,* candidate genes on chromosome 1q21 include SNX27, which is involved in endocytosis of plasma membrane receptors; KCNN3, a calcium-activated potassium channel, and HCN3, a cation channel. The localization on chromosome 15q24 also contains a number of possible candidate genes, including HOMER2, a gene involved with glutamate receptor function, AP3B2, involved in plasma membrane receptor endocytosis; and SH3GL3, which plays a role in CNS development.

The haplotype data in family A, however, raise the possibility that both loci are in fact implicated in the disease process. For example, an interaction between a novel, as yet unidentified mutation *CHRNB2* gene on 1q21 (presumably of borderline pathogenicity), and a mutation in a functionally related gene on chromosome 15q24, might be insufficient in isolation to cause ADNFLE but may result in the condition if inherited together. Digenic inheritance of this type has previously been described in a number of disorders. The first example in human disease was identified in families with retinitis pigmentosa, in which only individuals doubly heterozygous for mutations in the unlinked but functionally related photoreceptor-specific genes ROM1 and peripherin/RDS developed the condition (Kajiwara et al., 1994). Since then, convincing evidence of digenic

inheritance has been reported in various conditions, including Bardet-Biedl syndrome (Katsanis et al., 2001; Fauser et al., 2003), non-syndromic deafness (del Castillo et al., 2002), insulin resistance (Savage et al., 2002) and early-onset Parkinson's disease (Tang et al., 2006). To date, digenic inheritance has not been definitively identified in epilepsy, although evidence for this inheritance pattern from linkage studies was obtained in one family with febrile convulsions and temporal lobe epilepsy; no mutations has yet been reported in this family (Baulac et al., 2001).

Most examples of digenic inheritance show a digenic-diallelic mechanism, in which affected individuals are doubly heterozygous for mutations in different but often functionally related genes (Zheng et al., 2005; Tang et al., 2006); individuals with mutations in only one of the two genes are unaffected. In digenic-triallelic inheritance, which has been reported in a syndromic variant of Bardet-Biedl syndrome, two mutant alleles are required in one gene and one at another (Katsanis et al., 2001; Fauser et al., 2003).

In addition to the linkage data, the more severe phenotype seen in family A and B reported here is potentially in-keeping with digenic inheritance. A recent report of digenic Emery-Dreifuss syndrome was associated with an unusually severe disease phenotype (Muntoni et al., 2006), and a single case report of unusually severe Becker muscular dystrophy was associated with mutations in both the dystrophin and the functionally related Myf6 genes (Kerst et al., 2000). It is possible that such an association of two functionally-related genes, insufficient in isolation to produce the ADNFLE phenotype, in combination produce the more severe features observed in these families. While it might be anticipated that some mildly affected family members would carry only one of the relevant alleles, a finding not seen in family A, this is not necessarily the case. Indeed, in most conditions previously reported with digenic inheritance patterns, mutations in one gene only are insufficient to produce the disease phenotype. Possibly more difficult to explain, however, is the presence of asymptomatic obligate carriers in family A. If digenic inheritance is responsible for an exacerbation of the phenotype, intuitively it becomes more difficult to explain the presence of such individuals. While such concerns make the possibility of digenic inheritance less

compelling in this family, they do not refute it entirely; however, sequencing of potential candidate genes and identification of causative mutations will be necessary to validate this hypothesis.

Conclusion

Although ADNFLE is classically described as a condition with normal intelligence in which behavioural and psychiatric problems are either a misdiagnosis of the underlying condition or a social consequence of unrecognized seizures, evidence is emerging that this is not always the case. Our families, in conjunction with some previous reports (Cho et al., 2003; Magnusson et al., 2003; McLellan et al., 2003) suggest that psychiatric and behavioural problems, mental retardation and developmental regression may be part of the spectrum of this disorder, particularly in those individuals with very severe epilepsy. It is possible that certain mutations associated with ADNFLE confer a greater genetic predisposition to these features than others; the absence of any recognised mutation in genes coding for the neuronal nicotinic acetylcholine receptor and linkage to two loci raises the prospect of an alternative, possibly digenic, mechanism in the families presented here. Recognition of behavioural and psychiatric conditions in families with ADNFLE, as well as intellectual disability, is important as these problems may be a greater cause of suffering than the seizures themselves. Optimization of seizure control may help to minimize the impact of these comorbidities and improve outcome. Ultimately, molecular genetics may elucidate the relationship between frontal lobe epilepsy and the affective and cognitive disorders observed in these families.

PART 3:- GENERAL DISCUSSION AND CONCLUSIONS

CHAPTER 15
GENERAL DISCUSSION

The work in this thesis addresses three aspects of sleep and its relationship with frontal lobe epilepsy. First, (Chapter 11), changes in serotonergic neurotransmission were examined across the human sleep-wake cycle using the novel PET ligand ^{18}F-MPPF. Altered function in the neurotransmitter systems underlying normal human sleep may play a fundamental role in the precipitation of seizures in some epilepsy syndromes. The aim of this study was to look for measurable changes in serotonergic neurotransmission across the human sleep-wake cycle, and compare these observations with previously reported data from animal studies. The second aspect (Chapters 12 and 13) was the clinical and semiologial features of the NREM arousal parasomnias such as sleep terrors and somnambulism. These disorders may be easily confused with NFLE, and systematic descriptions of their historical and behavioural characteristics are scanty. Improving diagnostic accuracy is clearly important from a clinical perspective, but is also vital in genetic studies of ADNFLE – parasomnias represent potential phenocopies of NFLE, and may therefore undermine linkage analysis in this setting. The aim of these studies was, therefore, to clarify the clinical features of parasomnias, and to identify those which are of greatest value in discrimination from frontal lobe seizures. Thirdly, a clinical and genetic analysis of two large families with a severe form of ADNFLE was undertaken. Affected individuals in these families had severe, refactory epilepsy and high rates of intellectual disability and psychiatric or behavioural morbidity. Molecular genetic studies on the larger family have been undertaken by Assistant Professor John Mulley's group, based in the Department of Genetic Medicine in the Women's and Children's Hospital, Adelaide, Australia. No nAChR mutation has been identified at this time. While not yet conclusive, however, these studies raise the possibility of a novel mechanism for the severe ADNFLE phenotype observed here.

^{18}F- MPPF, serotonin and the sleep-wake cycle

Our understanding of the neurochemical basis of sleep has increased dramatically over the last few decades. An increasing number of neurotransmitter systems have been associated with sleep regulation, many of which have also been implicated in human disease. These neurochemical changes may be critical to the relationship between sleep and a variety of neurological disorders in man, including the epilepsies.

The current understanding of this area is, however, based almost exclusively on data from animal studies. From the early multilevel brainstem transactions studies, to more recent work using microdialysis and neurophysiological techniques (see literature review, Chapter 2, pages 43-50), the invasive and often destructive nature of the methods employed to study sleep neurochemistry generally precludes their use in human subjects. As specific REM and NREM sleep states are seen in all mammalian and avian species, mediated through phylogenetically preserved brainstem structures, it is usually assumed that the fundamental mechanisms of human sleep are similar or identical to those of other animals. However, direct evidence for this is limited, and such assumptions should be made with some caution. The development of PET ligands with apparent sensitivity to endogenous neurotransmitter concentration has opened new possibilities for studying physiological neurotransmitter flux in humans. The novel ligand ^{18}F-MPPF, a competitive antagonist of the $5HT_{1A}$ receptor, is the first serotonergic ligand which appears to demonstrate such properties.

What has been learnt

Serotonin and sleep. The experiment described in Chapter 11 examined serotonergic neurotransmission across the human sleep-wake cycle using ^{18}F-MPPF PET. The widespread increase in ^{18}F-MPPF binding identified in sleep compared to wakefulness indicates that serotoninergic $5HT_{1A}$ receptor availability is increased in sleep compared to wakefulness, although the precise interpretation of these findings is not straightforward. The simplest, and most intuitively attractive, interpretation is that serotonin release is greatest during wakefulness

and reduced during sleep, in line with existing animal studies. However, while this is one possible explanation, the mechanisms regulating ^{18}F-MPPF binding across the sleep-wake cycle may be more complex. A number of factors, including neurotransmitter release, neuroreceptor trafficking, and state-dependent alterations $5HT_{1A}$ receptor affinity, may influence ^{18}F-MPPF binding (see literature review, Chapter 3 pages 86- 87), and the precise influence of each of these is not yet clear. Nevertheless, the clear increase in $5HT_{1A}$ receptor availability observed during sleep is congruent with existing animal data.

^{18}F-MPPF PET. Although there has been compelling animal data to indicate that ^{18}F-MPPF binding is sensitive to supraphysiological endogenous serotonin release, some studies have suggested that normal physiological serotonin fluctuations might not be detectable using ^{18}F-MPPF PET (see literature review, Chapter 3 pages 86-87). The findings reported here, however, indicate that this technique is capable of detecting physiological changes in human serotonergic neurotransmission *in vivo*.

Future directions

Serotonin and Sleep. Replication of this study in normal subjects is important to confirm the applicability of the findings to normal human sleep. The subjects in this experiment all had narcolepsy-cataplexy; these subjects were chosen to maximize the chances of recording sleep during the scanning period, and because this disorder has not been associated with primary serotonergic dysfunction. Narcolepsy-cataplexy arises through loss of hypocretin-containing neurons in the dorsolateral hypothalamus. Although the wake-promoting effects of hypocretin may, in part, be mediated through stimulation of serotonergic and noradrenergic neurons (see literature review, Chapter 2, page 49), there is no evidence that serotonergic function is fundamentally affected in this disorder. It is, therefore, likely that the changes in serotoninergic neurotransmission observed across the sleep-wake cycle in narcolepsy-cataplexy are similar to those in normal human sleep, although this requires experimental confirmation. Studies of sleep in normal volunteers are logistically more difficult than in individuals with

narcolepsy. In many centres, scanning at night is impractical, but to have a reasonable chance of obtaining daytime sleep in normal volunteers a degree of prior sleep deprivation is often required. This process may itself influence serotonergic neurotransmission, a fact that would need to be taken into account in any such study.

Mechanism of altered ^{18}F- MPPF binding. From a technical perspective, more work is needed to understand the mechanisms of altered ^{18}F- MPPF binding observed here. At the simplest level, these changes may reflect displacement of ^{18}F- MPPF by endogenous serotonin, or receptor internalization in the face of endogenous serotonin release. However, the possibility of more complex interactions, including changes in receptor affinity states with the sleep-wake cycle, need to be considered (see literature review, Chapter 3, pages 86-87). Such questions are more easily answered using animal studies, as techniques including microdialysis, PET and β-microprobe, and autoradiography can be employed in combination in this setting.

Other uses for ^{18}F- MPPF PET. A wider role for ^{18}F- MPPF PET in the study of serotonergic neurotransmission *per se* still requires confirmation. Clear changes in ^{18}F- MPPF binding were demonstrated across the sleep-wake cycle in the current study, but ongoing investigations in a variety of settings are required. There are at least two potential factors which may limit broader applicability of ^{18}F- MPPF PET. The first relates to the magnitude of serotonin flux being studied. The variation in endogenous serotonin between wakefulness and REM sleep is probably the largest to occur during normal physiological function; serotonergic neurons are active during normal wakefulness, but their activity reduces considerably during NREM sleep and ceases entirely during REM sleep (see literature review, Chapter 2, page 45-46). It is possible that such large changes in serotonin concentration are detectable using ^{18}F- MPPF PET, but that smaller physiological, and even pathological, variations may not be. The second reason relates to sleep-related changes in $5HT_{1A}$ receptor affinity. It has been hypothesized by some authors that certain states, such as anaesthesia and potentially sleep, may lead to changes in receptor affinity unrelated to endogenous

serotonin release. If this is the case, such changes may be an essential component of the altered ^{18}F- MPPF binding observed during sleep in the present study. Changes in endogenous serotonin in other settings, unrelated to sleep, might therefore have no detectable effect on ^{18}F- MPPF binding. Further studies may be able to clarify these points. For example, a comparison of ^{18}F- MPPF binding pre and post SSRI administration (with both scans performed during wakefulness) might be a useful experiment to address the second concern.

If the reliability and sensitivity of ^{18}F- MPPF PET for detecting endogenous serotonin flux can be confirmed, it has the potential to become a valuable neuroimaging modality. Serotonin is believed to play a role in a wide range of neuropsychological functions including emotion and cognition, as well as neurological and psychiatric disorders including schizophrenia and depression. As such, any technique with the capacity to detect fluctuations in CNS serotonin *in vivo* would have extensive applications.

PET ligands, sleep and epilepsy. Finally, taking a broader view, ^{18}F- MPPF may be the first of many PET ligands with the potential to shed light on neurochemical changes in human sleep, and the relationship of these to epilepsy and other neurological disorders. For example, the serotonergic system has long been suspected of involvement in myoclonus. ^{18}F- MPPF PET may be useful for examining relationships between serotonin, sleep and myoclonus, particularly in conditions such as juvenile myoclonic epilepsy in which myoclonus is common on waking and is exacerbated by sleep deprivation. Likewise, ligands are emerging for other neurotransmitter systems involved in sleep, and may be used to study human sleep and its relationship to disease. Particularly interesting are the emerging $\alpha 4\beta 2$ nAChR ligands such as [^{18}F]-F -A-85380. The recently reported finding of altered [^{18}F]-F -A-85380 binding in ADNFLE, increased in brainstem and epithalamus but reduced in mesial frontal regions (Picard et al., 2006), is an example of how such studies may shed new light on the mechanisms of sleep-related epilepsies.

Distinguishing parasomnias and NFLE

Distinguishing NFLE from the NREM arousal parasomnias can be difficult; both conditions often present with unusual and dramatic sleep-related events, and investigations are often unhelpful. While misdiagnosis of NFLE as parasomnias has been widely reported (Scheffer et al., 1994), increasing awareness of this condition may also result in the opposite problem, with parasomnias being incorrectly diagnosed as epileptic seizures. Although the clinical features of NFLE have been extensively studied and well described, those of the NREM arousal parasomnias have not. While their existence and broad behavioural manifestations are well known in both medical and lay communities, descriptions of their clinical features remain nebulous, based largely on clinical anecdote and traditional descriptions. The absence of any systematic analysis of the historical features and ictal semiology of parasomnias contributes to the diagnostic difficulties which may arise in this setting.

What has been learnt

Two systematic studies of NREM arousal parasomnias are presented in this thesis; one is a study of historical data, the other a detailed examination of electroclinical features as recorded on video EEG monitoring. These studies are, to my knowledge, the first of their kind in parasomnias, and identify the principal clinical features of these conditions. In addition, direct comparison with NFLE has identified a number of key differences and similarities between these disorders.

Historical features. Analysis of the clinical histories in NFLE and parasomnias (Chapter 12) demonstrated that these disorders can usually be distinguished on the basis of the history alone. Interestingly, the data indicated that many individual clinical features are common to both conditions, and few features, if any, are entirely reliable discriminators when taken in isolation. However, when these are reviewed in combination, the disorders rarely closely mimic one another. This is reflected by the validity of the scale developed here (FLEP – Frontal lobe epilepsy and parasomnia scale), which predicts a diagnosis based on a composite of clinical

features. From the data presented, a confident diagnosis of NFLE or parasomnias could be made on the basis of the FLEP scale in over 80% of individuals. In the remainder, however, a diagnosis of epilepsy was suspected but was uncertain; such subjects would still require video EEG monitoring. Thus although previously most authors have emphasized the importance of video EEG monitoring in the diagnosis of NFLE (see literature review, Chapter 10, page 190), these finding suggest that such a diagnosis can often be made or excluded with confidence on the basis of the history alone.

Electroclinical features. The companion study (Chapter 13) comprised a detailed description of the ictal semiology of parasomnias as recorded on video EEG monitoring, and contrasted the findings with those of NFLE. Although numerous studies of semiology have been conducted in epilepsy, to my knowledge this is the first study of its kind undertaken in parasomnias. The principal finding was of three main behavioural patterns, which occurred either individually or, more commonly, in a combination within a single parasomnias event. These patterns ('normal' arousal behaviours, non-agitated motor activity, and distressed emotional behaviour), were broadly stereotyped both within, and to a lesser extent between, individuals.

In addition to these behavioural patterns, a number of elemental semiological features positively favouring a diagnosis of parasomnias over NFLE were identified. These included an indistinct offset, failure to rouse to full wakefulness, physical and verbal interaction with the environment, and prominent 'normal' arousal behaviours. Many characteristic features of NFLE, including bicycling automatisms, dystonic posturing, grunting respiration, and a clearly defined offset were rare in parasomnias. However, the study also demonstrated that some individual behaviours were indistinguishable in NFLE and parasomnias; this was a particularly striking with respect to initial arousal behaviour. Both seizures and parasomnias could commence with identical arousal behaviour of this type, lasting for several seconds prior to the major motor activity of the event. As a result, it would appear that brief nocturnal arousals cannot be diagnosed as epileptic or non-epileptic on the basis of semiology alone. In the absence of clear epileptic behaviours or definitive EEG abnormalities, additional information (such as sleep

stage, frequency of arousals and stereotypy) must be used to form the basis of a diagnosis, but these features are not entirely reliable.

In addition to the clinical applicability of these findings, the video EEG monitoring study also provided some clues to the underlying mechanism of parasomnias. The similiarity of the four main behaviour patterns within, and also between, individuals suggests they may be mediated by subcortical central pattern generators (CPGs). Such a mechansism has been invoked by several authors in discussions of epileptic automatisms, and it has been occasionally suggested that similar mechanisms may be responsible in NFLE and parasomnias (Tassinari et al., 2005). The findings presented in this study, however, indicate that while behaviour in parasomnias is very similar to *postictal* behaviour in NFLE, it is usually different to the *ictal* behaviour. This suggests that, although CPGs may be involved in both parasomnias and NFLE, the nature of their activation in these disorders may be quite different.

Future Directions

Although the existence of parasomnias such as somnambulism has been recognised for centuries, the understanding of these disorders is still limited. This is partly due to the rarity with which they are recorded in a monitored environment, and partly because, although sometimes distressing for onlookers and occasionally dangerous for sufferers (injury during sleepwalking is well described), they are generally considered to be quasi-physiological events, and not intrinsically pathological.

Nevertheless, parasomnias may have the potential to provide important information about mechanisms of arousal and sleep stage transition in the normal human brain. The strong family history in many subjects opens possibilities for genetic studies, with the potential to identify molecular mechanisms important in arousal. Modern imaging modalities, including fMRI and PET, may provide important insights into neural mechanisms of sleep and arousal, and comparisons of individuals with and without parasomnias may be instructive in identifying networks or anatomical structures involved in neuronal synchronization during

sleep. An increased understanding of such mechanisms may ultimately also provide insights into sleep-related epilepsy syndromes, including ADNFLE.

Finally, the role of CPGs in epileptic automatisms and parasomnias warrants further investigation. The similarity between the behaviour in parasomnias and postictal behaviours in NFLE was a striking finding, and further comparisons of parasomnias with ictal and postictal automatisms in other forms of epilepsy may be enlightening. Designing studies to prove or disprove a role for CPGs in these disorders is difficult at present, as the exact nature and extent of these networks in normal mammalian behaviour is not well understood (Kiehn, 2006). However, their structure and function of central pattern generators in mammals is an active area of basic science research; as the anatomical and physiological arrangements of these neural circuits are increasingly understood, this knowledge may be applied to the study of parasomnias and epileptic automatisms.

Severe ADNFLE – Clinical and genetic considerations

ADNFLE is usually considered to be a relatively mild epilepsy syndrome. While seizures may be difficult to control in childhood, they usually respond to carbamazepine in adults; comorbidities, such as cognitive and psychiatric disorders, are reported infrequently. Causative mutations in ADNFLE have been definitively identified in genes coding for subunits of the nAChR, although these account for only a minority of reported cases. More recently it has been hypothesized that polymorphisms in the corticotrophin releasing hormone (CRH) may play a pathogenic role in some families without recognized nAChR mutations (see literature review, Chapter 9, page 158).

What has been learnt

Clinical Features. In contrast to the phenotype usually reported, two families with ADNFLE are described in whom epilepsy was severe, often refractory to multiple anti-epileptic drugs, and associated with high rates of intellectual disability, behavioural and psychiatric disorders (Chapter 14). In some individuals the disorder was devastating, with status epilepticus and severe refractory seizures

accompanied by marked developmental regression. Psychiatric and cognitive comorbidities in these families were often disabling, sometimes more so than the seizures themselves.

Molecular Genetics. No mutation in nAChR subunit genes was identified in either of these families. The molecular genetics in the larger family is, however, complex. This family was initially identified a decade ago, although has since been extended. The initial molecular studies provided evidence for linkage to 15q24. At that time, the critical region was thought to include the *CHRNA3/CHRNA5/CHRNB4* gene cluster, but no mutation was identified (Phillips et al., 1998). The extended pedigree examined here again provides stronger evidence for linkage to 15q24 but with much better physical mapping data now available, the region identified now *excludes* the *CHRNA3/CHRNA5/CHRNB4* cluster. In addition, the segregation of haplotypes is consistent with linkage to chromosome 1q21 (the region including *CHRNB2*), although, LOD scores for this region fall well short of statistical significance and sequencing of coding exons of *CHRNB2* has failed to identify any mutation. The significance of these 2 loci is, at this stage, unclear, and a number of possible explanations exist, including non-nAChR related mechanisms and even a possible digenic basis to the condition. While mutations in nAChR subunit genes do not appear to be the cause of ADNFLE in this family, they have not yet been definitively excluded. Molecular analysis of the regions of interest on chromosomes 1q21 and 15q24 is ongoing, including sequencing of candidate genes.

Future Directions

Clincial studies. From a clinical perspective, the possibility of systematic neuropsychological assessment in ADNFLE should be investigated, with particular reference to frontal lobe functions. Although development and cognition is said to be normal in ADNFLE, subtle frontal lobe dysfunction may be easily overlooked. The high rates of intellectual disability in the families reported here raise the possibility that cognitive involvement, albeit to a mild degree, is more widespread in ADNFLE than is generally appreciated. This is a technically

difficult area as the functions of the frontal lobes are complex, and existing neuropsychological tests are not always reliable at detecting mild dysfunction of this sort (Stuss and Levine, 2002). However, a deeper understanding of any neuropsychological deficits may help to identify anatomical structures involved in the seizures of ADNFLE, as well as potentially improving the management of affected individuals.

Molecular genetics. Although ADNFLE is a relatively uncommon disorder, it has now been reported extensively from around the world (see literature review, Chapter 9, page 153-4). Known mutations, however, account for only a minority of reported cases. The recent findings of a mutation in the α2 subunit, as well as possibly pathogenic polymorphisms in the corticotrophin releasing hormone (CRH) gene, suggest that α4β2 nAChR dysfunction is not the only molecular basis for this disorder. Ongoing studies of large multiplex families with ADNFLE should continue with the aim of further elucidating additional mechanisms. Findings in such families may lead to a deeper understanding not only of ADNFLE, but of frontal lobe epilepsy in general. Findings from more severely affected families such as those presented here may also provide insights into mechanisms of psychiatric illness and cognitive function. Moreover, they may shed light upon the intriguing relationship between frontal lobe epilepsy and NREM sleep.

Concluding remarks

The studies presented in this thesis are a small contribution to the understanding of sleep and its relationship to frontal lobe epilepsy; they address the neurochemical changes fundamental to human sleep as well as clinical, electrographic and genetic aspects of NREM arousal parasomnias and NFLE. Much work, however, remains. New technologies, such as neuroreceptor-specific ligands for PET and fMRI, will undoubtedly enable more sophisticated study of neurobiological changes in normal human sleep. Motor disorders of sleep, including parasomnias, currently attract only modest scientific interest but warrant more active investigation. Study of these disorders is important, not only to gain a deeper understanding of the conditions themselves, but also because of the insights into underlying sleep

mechanisms which they may provide. Finally, although clinical and molecular genetic studies of ADNFLE have already profoundly influenced our understanding of epilepsy, this disorder may still have much to teach us. Further study of ADNFLE may not only shed further light on fundamental mechanisms of epilepsy, but may also help to unravel the relationship between sleep and epilepsy which has fascinated observers since the time of Aristotle.

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APPENDICES

Appendix A. Semi-structured questionnaire for interviews in subjects with nocturnal events (Chapter 12)

Background

- Information obtained from (state relationship of collateral history giver to the subject):
- Number of events seen by individual giving collateral history (1 or 2; 3-10; more than 10):
- How long ago was last attack witnessed (weeks/ months/years)
- Current age of patient

Clinical History

1) Age of onset:
2) Age of offset (if applicable)
3) Semiology of attacks
   a) Give a general description of the events
   b) Are the events associated with an aura? If yes, give a description
   c) Does the subject ever walk during the episode? In particular, describe extent of wandering (do they ever walk out of the bedroom?).
   d) Are there complex, directed behaviours (e.g. dressing, turning on lights etc) during the episodes? Give examples.
   e) Is there a history of abnormal stiffening (including dystonic posturing), tonic extension or cramping? Give a detailed description.
   f) According to the subject and witnesses, are the events highly stereotyped, broadly similar or variable in their manifestation? Describe further if necessary.
   g) Has tongue biting or incontinence ever been a feature of these events? If so, how frequently? Give details.
   h) Does the patient ever recall the events? If so, is it a detailed or a vague recollection? Give details of the patients reported recall, and how often it occurs.

i) Does the patient vocalise during the episode? Is it shouting/ screaming, incoherent speech or coherent speech? Give examples of the things that are said.

j) If speech is a feature, does the patient recall what they have said? If there is recall, is it full or partial?

4) The day after the events, are their any symptoms? In particular, is headache or fatigue a feature?

5) How frequent are the patients 'attack nights'? Express per week/, month or year. Give details.

- Maximum frequency (and duration of this period)
- 'Average' frequency

6) How many episodes occur in one 'attack night'?

- Maximum number
- 'Average' number

7) Do the attacks tend to occur in 'clusters' (i.e. many for a period of days – weeks, then periods with very few or none). Give details.

8) Are there any factors that seem to trigger the events? In particular stress, fatigue or intercurrent illness.

9) Is there a pattern with respect to the most common timing of attacks during the night? In particular is it just as they are falling asleep (first 0.5 hour of sleep), in the first 2-3 hours of the sleep period, other times or no pattern? Be as explicit with timing as possible.

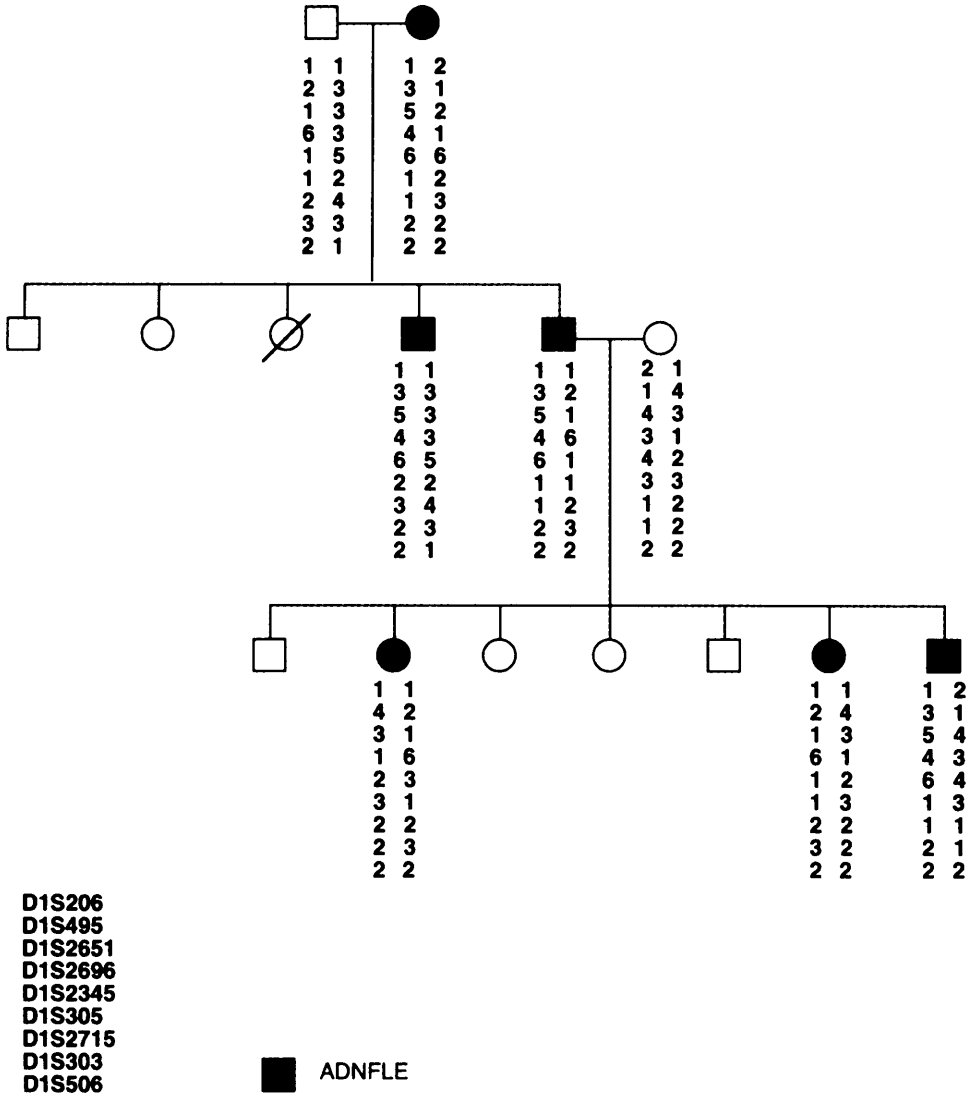
10) What is the duration of the events? Is there a lot of variability?

- Longest
- 'Average' or typical event

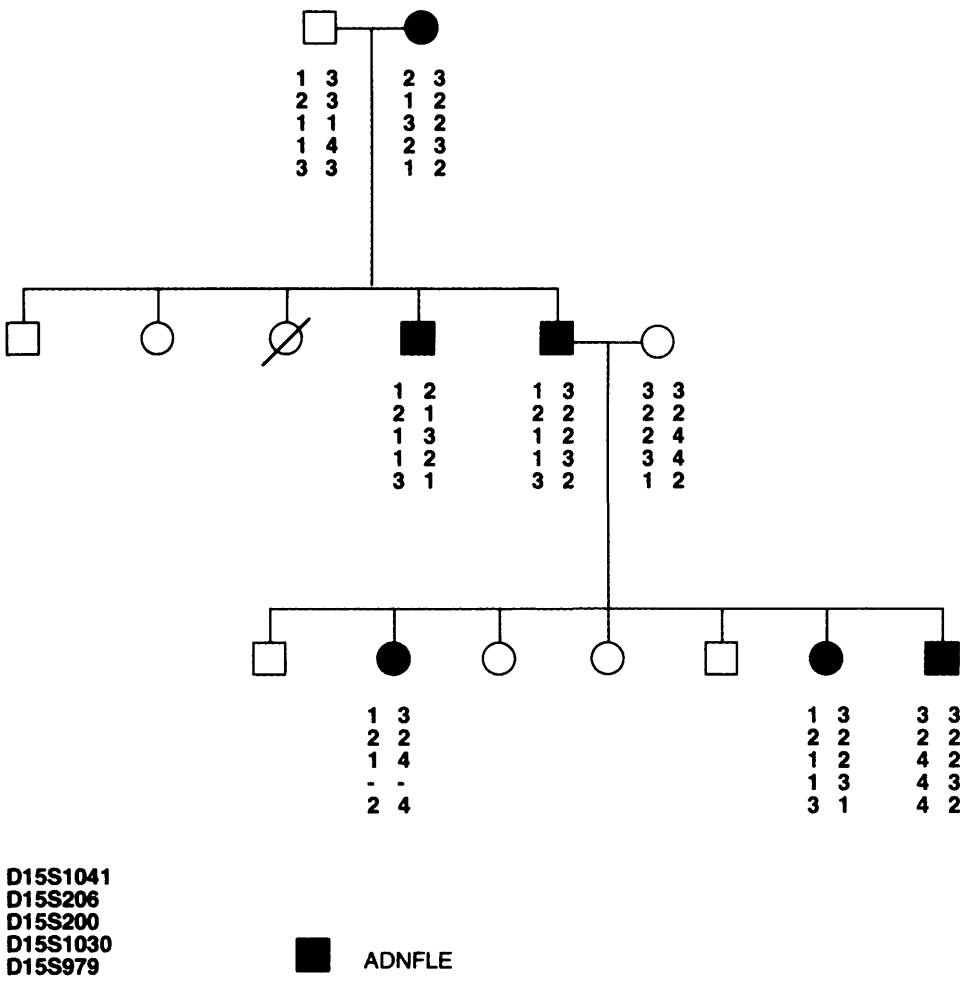
11) Additional information: is there a history of (give details):

- learning difficulties?
- behavioural disorder (e.g. ADHD) or psychiatric diagnosis?
- family history of nocturnal events?

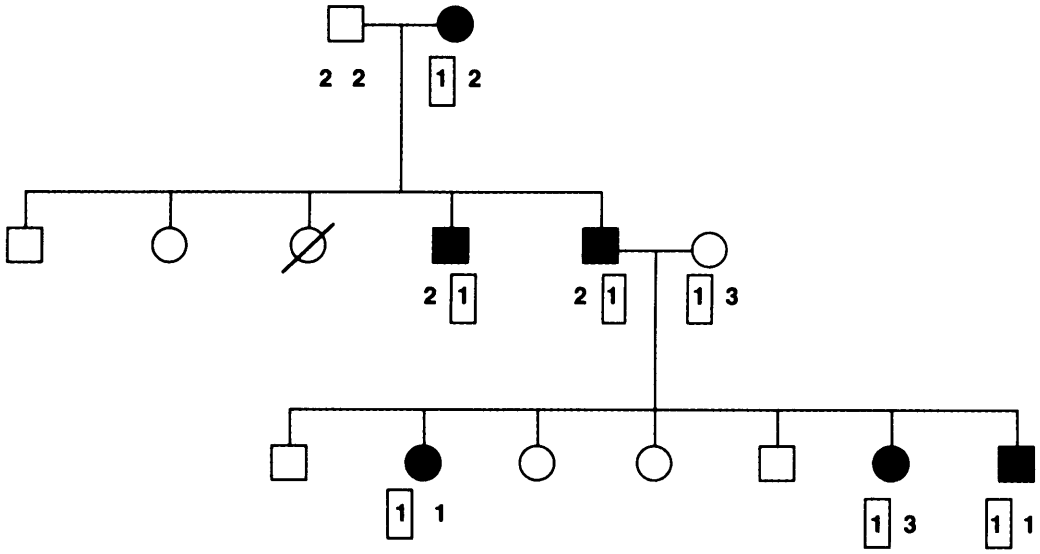
APPENDIX B . Haplotype markers in Family B (Chapter 14)



Appendix B.1. *Haplotype markers for chromosome 1q21 in Family B (Chapter14). Markers in this region do not cosegregate with ADNFLE*



Appendix B.2. *Haplotype markers for chromosome 15q24 in Family B (Chapter14). Markers in this region do not cosegregate with ADNFLE*



Appendix B. 3. *AC repeat marker in* CHRNA4 *in Family B (Chapter 14). Note that marker 1 is seen in all affected individuals, thereby* CHRNA4 *cannot be excluded.*